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THE SEQUELAE OF WAR HEAD INJURIES*

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BOSTON

EARLY in 1939, Air Commodore C. P. Symonds, consultant in neurology to the Royal Air Force and an authority on the subject of disability from head injuries, was planning the establishment of a central air-force hospital in England for neurologic problems from head injuries in flying personnel. He recognized the variety of special problems inherent in the assessment and adequate treatment of head injury in modern warfare, particularly the peculiar interrelation of surgical, neurologic, ophthalmologic and psychiatric problems involved. Colonel Hugh Cairns was, he found, already interested in neurosurgical organization for the British Army, and it was proposed that the two plans be coalesced in a combined services hospital for head injuries. Arrangements were completed with the enthusiastic co-operation of the Directors General of the Army and Air Force medical services, but not until some months after the outbreak of war did the hospital begin to take shape. It was eventually opened in February, 1940, as an army hospital with some specially seconded Royal Air Force personnel. It received both Army and Royal Air Force casualties. I had the honor of being placed in charge of the Medical Division, which was entrusted with the original plan of Air Commodore Symonds, closely interrelated with the Surgical Division to which Colonel, now Brigadier General, Cairns was consultant. Air Commodore Symonds was not only the consultant to the Medical Division but also organized and supervised the Registry of Head Injuries, which is making a most valuable research correlation of all the data made available by this unique unit.

The following account is concerned with the assessment and treatment of prolonged sequelae of head injury, although other types of neurologic disturbance also claimed attention. The surgical aspects of acute injuries have been commented on elsewhere.[1, 2] From the beginning, it was evident that, as had been foreseen, the proper treatment of the late effects of head injury under service conditions required a more than usually thorough preliminary examination. The large numbers of possible factors causing failure to return to duty following a reasonable convalescence from head injury (six weeks was the arbitrary time adopted) may be resolved into two chief categories — organic and psychoneurotic. It is essential to assess these factors accurately, for their treatment and disposal differ greatly.

The Registry has already collected complete data, including follow-up, on well over 1200 cases of head injury handled by the hospital. Complete analysis will ultimately be published by the British Medical Research Council, which finances this aspect of the work. The kind of problem involved can be estimated from my personal notes of the last 400 cases of persistent disability admitted by me for assessment. It must be emphasized that, although the hospital received acute head injuries from a large area and a majority of cases of persistent disability from all areas, these figures are highly selective, and complete data regarding all head injuries or all casualties cannot be published at present. I purposely omit the patients with recent injuries who made rapid recoveries. Out of the 400 cases of unduly delayed convalescence, 38 patients had suffered gunshot wounds of the head, 13 injuries to the head in aircraft crashes, 303 head injuries from other trauma (motorcycle or other accidents with vehicles, tanks and so forth), and 46 from recurrence of symptoms from old head injury dating from before the war. Of these 400 men, 22 (5.5 per cent) were suffering from *traumatic epilepsy*, 116 (29.0 per cent) from other *organic defects*, and 262 (65.5 per cent) solely or chiefly from *psychoneurosis*. In the group of 38 gunshot wounds, 3 pa-

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tients suffered from epilepsy, 19 were still disabled by organic (structural) disorders, and 16 by psychoneurosis. Of these, 21 were subsequently fit to return to duty, and 17 were discharged unfit. The proportion of the 400 returned to duty was almost exactly the same.*

It is clear that disorders such as hemiplegia and aphasia following a laceration of the brain are the result of damage to structure; on the other hand, a prolonged disability, such as insomnia, tremors, depression and fear of crowds, following a trivial head injury in a person who was previously prone to such symptoms is palpably psychoneurotic. The actual decision is, however, seldom so clear cut, and with increasing experience of all classes of injury from a variety of circumstances, more and more involved mixtures of organic and functional sequelae were defined by modern methods. Thus, to quote extremes, the aircraft pilot who has made a perfect recovery from a surgical head wound, has shown himself fit for every form of strenuous physical exertion, and pesters everyone to be allowed back to duty may develop a serious flying error on return to his squadron owing to a previously undisclosed nervous anxiety caused by the terrifying circumstances of his accident. Apart from the danger of further accident, the subsequent treatment for this neurosis involves a waste of time that is saved if the liability is diagnosed earlier. The patient who has suffered an apparently trivial head injury and later wanders, with loss of memory, is sometimes shown by the electroencephalogram or subsequent attacks to be suffering from epilepsy, although his original wandering fugue was hysterical and his memory is recoverable under Amytal. The patient behaving in a clearly neurotic manner may be found to have a xanthochromic spinal fluid, and the real reason for the failure to return to efficient duty of a patient with optic atrophy in one eye may be related not to his vision but to his anxieties about his relatives at home. An unsuspected abscess may be discovered by a chance air encephalogram, and an unsuspected but fundamentally important emotional factor may slip out in a casual remark.

Moreover, in the modern soldier, the tremendous tension of modern warfare — the noise, the rush of movement, the variations in climate and, above all, the heightening of individual responsibility — renders accurate assessment of great value in the decision regarding the return to duty and the kind of duty; such a decision is even more important in the airman, and may present the utmost difficulty in officers and commanders. When downgrading of responsibility appears desirable on medical grounds, or when the question of invaliding out of the service arises, further psychologic considerations complicate the picture and must be carefully weighed regarding individual personality if successful adjustments are to be achieved.

The medical services of the United States are no doubt fully alive to and prepared for the inevitable problems that will arise in these respects, but discussion of them, in the light of over eighteen months' experience of this kind of work before I was transferred to my present assignment, may be of interest.

General Considerations

Traumatic Epilepsy

The incidence of traumatic epilepsy following head injury will no doubt be a surprise to some, especially in view of the low figures of Sargent[3] after World War I (4.5 per cent in 18,000 cases) and of Stevenson[4] (1.5 per cent in 17,300 cases). But in the present whole series, the incidence was even higher than in the 400 cases mentioned above, for the Registry had filed 53 cases (16 focal and 37 generalized) out of a larger group of 630 fully documented consecutive patients. Of these, 22 had had attacks within one month, 16 in one to six months, 8 in six to twelve months, and 5 in two to five years. Of the 22 having convulsions within one month, only 6 had suffered gunshot wounds.

Traumatic epilepsy is a complication of localized destruction and scarring of cerebral tissue, particularly from so-called "open injuries," when the dura has been penetrated. The attacks had rarely remained sufficiently localized to give good results from excision of the scar (1 case in 400 head injuries, and this was a closed head injury). Closed head injury undoubtedly can give rise to traumatic epilepsy, as Symonds[5] has remarked; but the liability to epilepsy is not proportional to the severity of injury, even with prolonged unconsciousness and resulting intellectual defect. Of 87 patients with post-traumatic amnesia longer than seven days, only 3 suffered from epilepsy (2 generalized, 1 focal). One of these had shown evidence of focal brain injury, and it is likely that this was present in the other 2. Traumatic epilepsy is therefore not the result of a generalized damage to the brain. These figures are in accordance with those of Ascroft,[6] who analyzed material from World War I after an interval of seven to twenty years; in his series, the incidence of epilepsy was 34 per cent and, in cases in which the dura had been penetrated, 45 per cent. In other series, Wagstaffe[7] found a general incidence of epilepsy in 10 per cent of 377 cases, Rawling[8] in 25 per cent of 425 cases, and Credner[9] in 38.2 per cent in 1990 cases after five years. Cred-

*Symonds has published in the July, 1942, issue of the *Proceedings of the Royal Society of Medicine* the results of a follow-up of 871 cases, including the 400 mentioned here, that show 68 per cent successful return to service duties.

ner noted that 81.1 per cent of cases with dural penetration develop epilepsy. The variability of these figures depends on the manner of selection of the head-injury series, and the length of time under observation. The Registry will afford more accurate statistics as time passes. It must be borne in mind that the material discussed here includes few mild head injuries (concussion with full recovery within six weeks) and not many of the severer injuries, and consists of selected problem cases of intermediate type.

This situation is serious, and few surgeons appreciate the disabling possibilities of the simplest dural wounds. The problem is even more complicated in the common type of modern bomb or splinter injury, in which small fragments of metal and bone scatter widely through the brain, and lodge in the most inaccessible places. Such foreign bodies appear to cause no trouble, for they are seldom infected, and after débridement of the most superficial, the others may remain until more is known about their epileptogenic properties. So far as present hypothesis goes (Penfield[10]), it is the cerebrodural scar that is epileptogenic, not necessarily the foreign-body reaction, and experience with these very small splinters of bomb casings certainly bears this out.

The finding of Wagstaffe,[7] Symonds[5] and Ascroft[6] — that epilepsy occurring within the first four weeks after injury has an excellent prognosis — was fully borne out in our cases. The electroencephalogram shows widespread activity of epileptic type in many cases of laceration of the brain without clinical evidence of convulsions (Williams[11]), and this also rapidly subsides without aftereffect. There is, however, an exceptional and rare type of case in which a relatively trivial injury has been followed by persistent severe fits of a generalized kind, with an electrical record in the intervals between the attacks resembling that of deteriorated idiopathic epileptics. A previous constitutional liability to epilepsy is then to be suspected, and the prognosis is poor.

Other Organic Disabilities

Of the other consequences of structural damage to the brain, hemiplegia, paraplegia from wounds to the vertex, hemianopia or scotomatous field defects and dysphasic-dyspraxic disorders are obviously serious disabilities. Much can be done to rehabilitate such men for some form of civilian employment, with training in special skills. The same training facilitates the speed of recovery of lesser disorders of motor function, sensation, speech and vision. Persons who are really effective in designing exercises in muscle re-education, or to obtain sensory co-ordination, and who can direct speech therapy and visual exercises are few. Moreover, such treatments are time consuming. The experienced physician therefore early selects cases with a good prognosis for return to duty and retains them in the service hospital, advising early discharge of the remainder to civilian rehabilitation centers. The general nature of the problem is well described by Goldstein[12] in a monograph in which he summarizes his experience in World War I. He gives an excellent description of methods again found useful both in accurate assessment and in rehabilitation. It is not practicable to rehabilitate all men in a service hospital that has a large waiting list.

In cases requiring bony repair, with fractures into a frontal sinus,[13] with retained foreign bodies, and with jaw, facial, ophthalmic and other injuries, surgical consultations and conferences regarding the main disability are indicated; if necessary, the patient is transferred to a surgical division, to return later for the neurologist's supervision during final convalescence. In some cases of recent injury (and usually in hitherto unsuspected scalp wounds), a subdural hematoma, an abscess or necrosis of the bone requires direct surgical relief.

Post-traumatic General Cerebral Syndrome

Prominent in the sequelae of head injury are headache, usually associated with vertigo, difficulty in concentration and insomnia, with or without depression. This whole group, variously described as the "postconcussion syndrome," "post-traumatic general cerebral syndrome" (Foerster[14]) and "minor contusion syndrome" (Symonds[15]) is by far the commonest symptom complex that develops out of craniocerebral injuries. It follows all kinds and degrees of head injury, although many writers have commented on its absence in many cases of severe laceration of the brain (Russell,[16] Schaller,[17] Strauss and Savitsky[18] and others). A general discussion of the symptoms is given by Symonds.[15] Schaller[17] subdivides cerebral post-traumatic disorders into the "post-traumatic psychoneurotic state," with symptoms of headache, dizziness and hysteria, and the "post-traumatic concussion state (encephalopathy)," with loss of concentration, defective memory and vertigo. This presupposes that headache, dizziness and so forth are psychoneurotic symptoms, and some frankly ascribe the combination to a compensation motive. Others[16, 19] have pointed to its occurrence in cases without compensation factor of any kind. The subject has been very adequately reviewed by Strauss and Savitsky.[18] Penfield and Norcross[20] claim that post-traumatic headache is due to meningeal adhesions demonstrable by their special

technic for showing subdural air, and that "the patient's description of his symptoms makes the diagnosis certain and allows the understanding physician to recognize the true sufferer." They do not specify the elements in the description on which this sanguine statement is based. It is probable that headaches of organic and psychoneurotic types should have different clinical characteristics. With my associates, I attempted, unsuccessfully, to define such differences as may exist. We found that clearly demonstrable meningeal scarring was occasionally the site of localized ache, but usually not. Subdural air has been seen in encephalograms without previous injury (Lemere and Barnacle[21]) and is not regarded as of value in diagnosis. On the other hand, the depressed psychoneurotic patient frequently complains of a steady, dull discomfort over the whole head, unaffected by posture or external events, except excitement. This type of headache is well recognized as of psychoneurotic origin. But this was not the answer. The common paroxysmal generalized or one-sided headache — diffuse but usually frontotemporal, affected by posture as well as exercise or excitement, rising to intensities of sharp pain followed by numbness, and associated with swimminess on or after stooping, with loss of concentration and, usually, periodic insomnia — was as commonly associated with frank psychoneurosis as with severe brain injury. One difference, however, that probably accounts for the denial of many that such a post-traumatic syndrome is associated with severe head injury, is its delayed onset in these cases, so that at the time of discharge from the hospital or the completion of usual convalescence, the syndrome has not yet appeared.

Among other names, the group of symptoms is commonly called the "post-concussion syndrome." If by concussion is understood immediate loss of consciousness due to injury of the head, associated with loss of memory for this time, and retrospective loss of memory of the injury and the events immediately preceding it, it is certain that the post-traumatic general cerebral syndrome can occur without concussion.

Something must be said of the pathology of concussion. Experimental evidence has shown that concussion is not associated with any cerebral lesion recognizable by the naked eye, or by the microscope with any staining process at present available.[22] It is not due to any effect on cerebral blood vessels, although changes in circulation accompany its later stages. It has a characteristic effect on the cerebral electrical record,[23] and is a phenomenon common to any nervous center subjected to sufficiently sudden physical stress. It is a transient paralysis of nervous function. In head injury, it is generalized, and is produced by sufficiently sudden acceleration or deceleration of the head. It is thus often absent in crushing injuries, even though they cause multiple fractures and other damage,[22] for the head may not be subjected to change in velocity.

It is common knowledge that extradural hemorrhage, subdural hemorrhage or cerebral contusion can be produced by an injury that does not concuss the patient. These effects are due to local tears or distortions. Clinical evidence shows that medullary contusion, with or without subarachnoid hemorrhage, can be produced without concussion.[24] In war surgery, the absence of concussion in penetrating injuries of the brain has been commonly noted (Léri,[25] Denny-Brown,[24] Denny-Brown and Russell[22] and Eden and Turner[26]). Concussion is the outcome of *general commotion* of the brain, which is slighter or absent when penetration occurs, especially with small fragments.

Recently, fat embolism has been held responsible for concussion (de Gutiérrez-Mahoney[27]). This, however, did not occur in my experimental work on concussion.[22, 23] Furthermore, the recognized clinical disorder due to fat embolism is delayed in onset and characterized by unmistakable features in pathology (Osnato and Giliberti[28] and Robb-Smith et al.[29]). In all the cases of acute head injury in this series, there was only 1 patient who clearly suffered from fat embolism — that is, fever, petechiae and fat in the urine. The patchy damage it causes in the cerebral cortex is identical with the patchy cell changes in the cerebral cortex found months or years after injury that are described by Winkelman and Eckel[30] and that are considered by them to be the basis of the post-traumatic general cerebral syndrome.

The common types of severe head injury show various combinations of a series of separate clinical entities, including medullary contusion, subarachnoid hemorrhage, general cerebral concussion, cerebral contusion, laceration, intracerebral and extracerebral hemorrhage, subdural collections of blood or fluid, skull fracture and, sometimes, fat embolism. Each or all may be followed by the syndrome in question. Despite the influence of posture, one should regard the syndrome at this stage as a *particular mode of reaction to head injury*, without specific identification with either an organic or a functional basis. In this sense, it is directly comparable to the "effort syndrome," recognized by Wood[31] and others as related to either cardiac disease or cardiac neurosis and, in both, a type of reaction to cardiac symptoms. Only in this way does it appear possible

to reconcile the appearance of the post-traumatic syndrome in association with a great variety of types of injury. Some illustrative examples indicate the general nature of the problem.

Case 1. Driver R. L. B., aged 21, was thrown from an army car on January 10, 1940. There was a retrograde amnesia for a few seconds and a blank in memory for 10 minutes after the injury. The patient then vomited and was taken to a hospital. There was a bruise in the right temporal region, but no other injury. Right-sided headache continued for 3 days and then ceased. The patient felt well and was discharged to duty after 3 weeks. In May, after 10 days of continuous fighting, he became very exhausted and once fainted for a few minutes. He came through Dunkirk without incident but a month later began to suffer from generalized headache every 3 or 4 days lasting all day, more pronounced with exertion or excitement, and associated with dizziness on movement. In the next month, he fainted four times, usually after some physical exertion. His mother and a cousin had suffered from psychoneurosis, and his mother had fainted on several occasions. He had been an average scholar, had always been a worrying, sensitive fellow, and had once fainted at a camp at the age of 12 years.

He was of pale complexion and poor physique, but had no sign of injury to the head and no abnormal physical signs. X-ray films of the skull showed no bony injury. An electroencephalogram was normal. The red-cell count was 4,175,000 with a hemoglobin of 85 per cent. After prolonged interviews, the patient recollected being terrified of traffic after his accident and had vivid recollections of it for some weeks. He explained how he then became less nervous, but after Dunkirk had vivid recollections of the fighting and became terrified of the possibility of pain or the sight of blood. He said, "I could not go through that again." He developed fears of traffic or air raids, and had nightmares of falling and of being wounded. He was sure that he had fractured his skull and damaged his brain.

He responded immediately to psychotherapy but relapsed, with further headache and complaint of dizziness at the prospect of return to duty, and was eventually discharged as permanently unfit.

This patient presented the post-traumatic syndrome in characteristic form, with typical postural reaction to the headache and even syncopal attacks, yet the vasomotor instability had antedated the relatively slight injury, and the whole syndrome was considered to be a result of constitutional psychoneurosis.

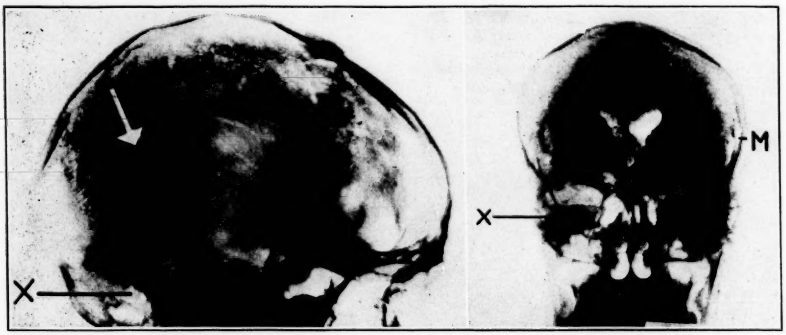

Figure 1. *Case 2.*

In the lateral view of the skull, just below the arrow, is a small puncture of entry of the bomb fragment, with underlying gray flakes of bone and small metal particles. The main metal fragment had crossed the cavity of the skull to lie on the tentorium, where it is seen through the mastoid cells (to the right of the line x*). The anteroposterior view, with the ventricles filled with air, shows enlargement of the ventricle on the side of entry and the metal fragments (*m *and* x*).*

Case 2. Corporal Y., aged 22 years, sustained small cuts in the scalp from fragments of a bomb in May, 1940, and was concussed for 5 minutes. The scalp wounds healed rapidly, and he did not complain of any further disorder. In August, during another bombing, which did not harm him, he developed headaches on exertion, dizziness on bending, emotional lability and insomnia. These symptoms increased in intensity, and after 4 months of disability from them, examination revealed an excessively nervous man without sign of damage to the skull or nervous system. He admitted tremor during the second bombing, and that he had at that time deserted his post to take cover, even though he had not been discovered. He confessed inability to face further service, and further disclosed a matrimonial tangle of considerable proportions. X-ray films disclosed, unexpectedly, several bomb fragments in the brain (Fig. 1) and a small parietal portal of entry only a few millimeters in diameter. The patient failed to make adequate response to psychotherapy, and since there was a family history of severe nervous breakdown, he was discharged.

In this case, in spite of the presence of foreign bodies, the post-traumatic syndrome was considered to be purely psychoneurotic.

The following case is an example of local cerebral contusion without concussion.

Case 3. Guardsman A. C., aged 23, was injured on May 15, 1940, defending a canal bank at Louvain. He was struck tangentially by a bullet, which tore a 7.5-cm. hole in his steel helmet and made a cut 3.5 cm. long in the midoccipital scalp, 5 cm. above the occiput. He did not lose consciousness, and fired three more shots, but could not see plainly — "like through a mist." He crawled back to a trench and walked a mile to his medical officer. In this time, his vision was becoming dimmer, and when he arrived at his dressing station he could not distinguish light from dark. The wound bled severely and after morphine the patient remembered no more until 2 hours later, when he awakened in a casualty clearing station with severe headache but could see a little better. For

Figure 2. *Case 4.*

The lateral view of the skull shows metal and bone fragments. The portal of entry is very small and partly obscured by the lowest metal fragment. The ventricles were partially filled with air, and the patient was lying occiput down, so that there is a fluid level. The anteroposterior view shows distortion of the ventricle toward the fragments. All disability was nevertheless relieved.

the next few days, intermittent, severe frontal headache, radiating to the nose, lasted for hours and continued for the next 3 weeks, at first daily, with three bouts in the last week. Vision slowly improved, at first for near objects, with a shimmering mist blurring anything farther away than his own hand. No hallucinations occurred. The headaches usually appeared in the afternoons, and were immediately made worse by any movement. At other times, a cough caused a sharp stab but no lasting pain. Bending made the pain worse; later, the patient was more comfortable when lying down. In the 4th week, he could read small print, but the effort precipitated headache. In the 6th week, reading no longer caused headache, and his distant vision was clear for the first time. Headache on exertion became very infrequent, although of the same type and lasting for some hours. By the 9th week, the

Figure 3. *Private W.*

These are lateral and posteroanterior views of the skull of a patient who was not concussed by the penetrating bomb fragment, which crossed the frontal lobes to lodge above the opposite orbit. Flakes of bone lie directly beneath the point of penetration. After débridement, including removal of the bone flakes but not the metal fragment, he made an excellent recovery, without epilepsy or other disability.

patient had ceased to have headache except after very severe exertion or excitement, and felt well in all other respects. There had been no faints, and he had slept well all through. His vision was 20/30 in each eye, there was no field defect, the wound had satisfactorily healed, and x-ray films showed no bony damage. After a graduated convalescence, he returned to duty and remained well for at least a year.

This patient evidently suffered a contusion of the occipital lobes, but was not concussed. The local

brain injury conditioned a post-traumatic headache, but at no time was there any symptom that could be construed as being emotional or psychoneurotic. The subsidence of the headache paralleled the disappearance of the contusion as judged by the disappearance of the visual symptoms.

A similar history, with concussion and brain injury and spontaneous recovery follows:

Case 4. Private R. W. D., aged 21, was injured in Flanders on May 22, 1940. He remembered the whistling of a bomb and that he threw himself on the ground; he remembered vaguely an explosion and lifting sensation and then nothing until he was being bandaged with a field dressing less than 5 minutes later. His steel helmet had been blown off by the bomb explosion, and he had a scalp wound; he had difficulty in expressing himself, although he was well aware of his surroundings. He had headaches but no giddiness for the next 2 weeks. After 2 weeks, he could speak a few words, and gradually his speech returned completely in the next 2 months. He had at no time any difficulty in understanding written or spoken speech or in writing what he wished to say. After 3 months, he complained only of headache after severe exertion. Examination at this time revealed a slight right facial weakness, and a stellate scar in the left frontoparietal region, but no other abnormality. Speech was occasionally hesitant. X-ray films showed a small opening in the left parietal bone, with small fragments of bone and bomb splinters in the brain and with some enlargement of the ventricle by the resultant scar, as shown by air encephalograms (Fig. 2). Electroencephalograms showed a persistent low-voltage-wave focus just posterior to the wound of entry. No further surgical treatment was advised, and with graduated exercise the patient was entirely free from headache by October, returning to duty in November. He had remained well when last heard from, approximately 6 months later.

The patients in Cases 3 and 4 had excellent personal and family histories, and this no doubt contributed to their complete recoveries, despite severe local brain injury. They were cited to show that contusion, concussion, foreign bodies and even scarring of the brain substance are not necessarily factors in inducing continued headache. Furthermore, "organic" headache is not necessarily associated with postural giddiness. There were a number of other similar cases of gunshot penetration with complete recovery. In one such patient, a fragment traversed both frontal lobes (Fig. 3).

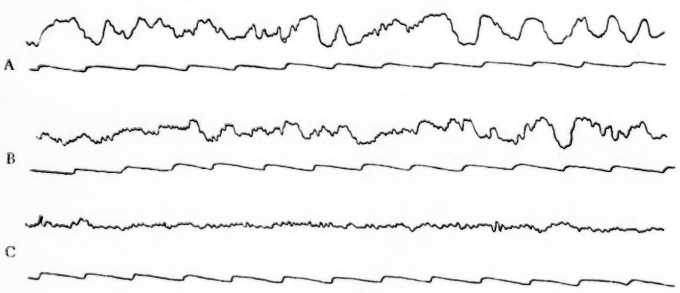

Figure 4. *Case 5.*

These electroencephalograms were made from bipolar parietal leads on the left side: A, seven days after the injury, B, three weeks after the injury, and C, ten weeks after the injury. The time tracings show 1-second notches. The disturbance was identical in all other leads on both sides at each stage.

Three cases of transverse through-and-through bullet wounds of the frontal lobes showed severe intellectual impairment but no evidence of post-traumatic syndrome. Other cases, with severe paralysis, also failed to develop the syndrome, but possibly because the disability prevented exertion, which is one of the provocative factors.

Another type of case, however, is more frequently associated with persistent post-traumatic syndrome, and in its severest form is usually called "traumatic delirium" or "traumatic stupor,"[32] according to whether or not restlessness is prominent.

Case 5. Sergeant R., aged 24, sustained a bilateral wrist fracture and a scalp bruise on the right temple in a motorcycle injury on November 14, 1940. He was admitted in coma,* with bleeding from the right ear. The pupils were small and equal, the tendon jerks brisk, and the plantar responses flexor. The pulse was 128 to 132, and the blood pressure 135/90. After 24 hours, the patient responded to questions by inarticulate noises, and resented interference; there was photophobia, and the plantar responses became extensor. After 4 days, he began to make intelligible remarks, such as "What's that?" "Don't do that" and "Is Mother there?" He was deeply confused,

*The Committee on Brain Injuries of the British Medical Research Council has compiled a standard definition of terms commonly used in head injury.[28] Coma or semicoma is preferred to "unconscious," and defined in terms of reaction to stimulus.

and the next day, in response to the question about how he felt, said: "Not too bad, doctor. I go to the hospital every morning." His restlessness increased, especially at night, and he shouted if interfered with. He was doubly incontinent. After 14 days, he could mumble his name and address in response to questioning, and occasionally showed his teeth or followed a finger with his eyes, if requested. The plantar responses returned to normal, and the incontinence lessened and disappeared. The patient remained grossly disoriented in time and place, and had

FIGURE 5. *Case 5.*

These lateral and anteroposterior views (occiput down) of the skull, after air encephalography, show general dilatation of the ventricular system.

no memory of the day before, or even what meals he had had that day. X-ray examination of the skull was entirely negative. The cerebrospinal-fluid pressure was 170 mm., and the protein was 35 mg. per 100 cc.; no cells were present.

Gradually, co-operation and orientation returned, passing through a stage of confabulation, with some perseveration in speech and ideas but no dysphasia. The memory was severely affected, and the patient often relived events of years or months before. Christmas Day, in the 6th week of his illness, was the first current event to remain in his memory and also subsequently marked the end of post-traumatic amnesia. The retrograde amnesia, at first of 3 months with "islands," gradually narrowed down to an irreducible minimum of a week.

The patient steadily improved, but with persistent slowness and difficulty in concentration. His memory remained grossly defective (except for retaining serial digits, but he had been an accountant). He was emotionally labile and disturbed by his difficulty in concentration.

Not until he began to get up each day did he complain of headache, generalized, increased by movement, concentration, noise or cough and lasting for some hours on his return to bed. He felt giddy if he turned quickly, and occasionally faint. When, after some weeks, he was given graduated exercise, he reacted by a "catastrophic reaction," failing suddenly on every test at an easy stage, and became depressed and introspective. Only with return to lesser grades and with great patience was he induced to further graduated activity. When well enough to care for himself, he was discharged for further rehabilitation in a civil hospital.

Throughout his illness, this man showed gross electroencephalographic abnormality. Large slow waves at the rate of 1 per second were present throughout the two hemispheres for the first fortnight (Fig. 4), and then gradually lessened with the appearance of faster rhythms. After 3 months, the base line still showed traces of the slow waves. There was not at any time a focus of abnormality.

This patient never showed any evidence of damage to a localized part of the brain. There was no evidence of fat embolism, although the urine was not examined for fat. The cerebral disorder was generalized and severe, and was followed by persistent intellectual deficit. It is an open question whether the emotional disorder and the post-traumatic syndrome were directly induced by the injury or were a psychoneurotic reaction to the patient's awareness of his mental limitation. The family and past histories were irreproachable; he had been a successful businessman before enlistment. An air encephalogram after 3 months showed generalized dilatation of both lateral ventricles, indicating generalized cerebral atrophy of mild degree (Fig. 5). In view of the persistent electroencephalographic abnormalities, which after 3 months took the form of small runs of slow waves at times (possibly indicating some tendency to epileptiform manifestation), the whole disturbance was regarded as directly consequent on the traumatic damage to the brain, and visualized as an extreme example of concussion.

Slighter varieties of this type of disorder, which might be called traumatic coma followed by confusion, are not uncommon. All degrees are met, down to such brief events as are more usually termed concussion, with correspondingly lesser degrees of, or absence of, residual intellectual impairment. An intermediate degree is illustrated by the following case.

CASE 6. Gunner J. B., after a motorcycle accident, was deeply comatose for 24 hours, and confused and restless for 21 days, with normal cerebrospinal-fluid pressure and contents. The electroencephalogram showed large slow generalized waves all this time. After a slow convalescence, — 3 months, — the patient was able to saw logs without symptoms. The electroencephalogram was not quite normal, and all memory and other intelligence tests gave a poor response (for example, the patient retained only six digits). On return to duty after 4 months, never having had a headache, he immediately broke down, became very emotional, complained of severe headache on any exertion and of giddiness on bending or turning suddenly or on looking up or down, insisted that he was

anxious to return to duty, and rapidly responded to psychotherapy. At the urgent request of his commanding officer, he was allowed to return to duty after further convalescence, subsequently relapsed and was eventually

to one or both of two factors: unduly prolonged coma and confusion following the injury, indicating concomitant severe generalized disturb-

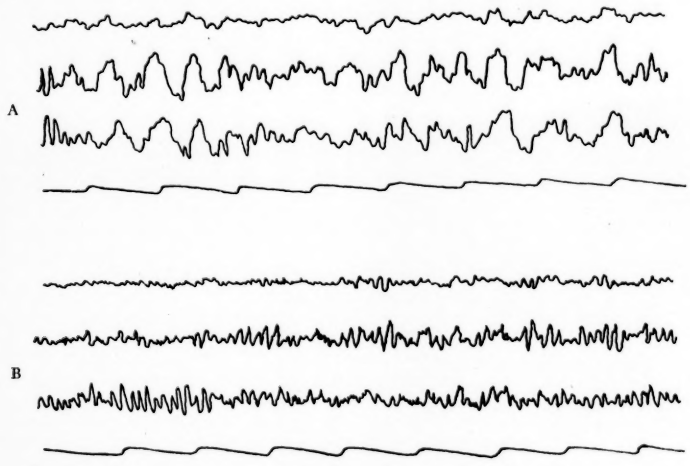

FIGURE 6. *Case 6.*

Each of these two sets of electroencephalograms was made from frontal, parietal and occipital leads, placed from above downward: A, *twenty days after the injury, and* B, *five months after the injury. The time intervals are one second apart. In* B, *traces of 2-second and 3-second waves are still seen.*

invalided permanently unfit. (This case has been reported fully, with electroencephalographic records, by Williams.[24]) The electroencephalogram still showed traces of slow waves at 3 to 8 per second after 5 months (Fig. 6).

The ultimate breakdown in this case was clearly psychoneurotic and was conditioned by anxiety about the future. Nevertheless, it must be admitted that a certain degree of impairment of judgment could still be demonstrated by careful tests, that the patient always had been a poor scholar, although his family and personal histories were otherwise good, and that such intellectual impairment as directly resulted from the injury may in fact have been the only cause of the failure to reattain an already limited adaptation to army life.

One may contrast patients who suffered comparable direct cerebral gunshot injuries, both perhaps with some slight residual disability, and whereas one made an excellent recovery, the other was held back by general post-traumatic symptoms. The failure of the second was regularly traceable to a history of liability to psychoneurosis or failure in adaptation in the personality or family history. In this group also fall the morons and chronic psychopaths whose capacity for adaptation is already limited.

(To be concluded)

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ACUTE PERFORATION OF ULCERS OF THE STOMACH AND DUODENUM

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RICHARDSON[1] reviewed the subject of acute perforation of ulcers of the stomach and duodenum from the data available at the Massachusetts General Hospital up to 1916. It is our purpose to present a study of the records of such patients from that date up to and including the year 1940. Richardson reported 103 cases with a mortality rate of 44.2 per cent. At the time of his writing, it was evident that the diagnosis was rarely difficult and that the best immediate results were obtained by simple closure of the perforation. There was at this time, however, a definite predilection for concomitant gastrojejunostomy in the good-risk patient. Moreover, the methods used for removing the extravasated fluid from the abdomen were variable. These technical differences persisted to some extent through the next decade. The last three five-year periods under discussion in our presentation, however, are comparable on the basis of the technic used, and were almost completed by the time the use of the sulfonamides had become common practice.

In the twenty-five-year period from 1916 to 1940, there were 334 admissions to our clinic with acute perforation of an ulcer of the stomach or duodenum. The diagnosis in all but 4 of these cases was confirmed at operation or autopsy. In one of the 4 exceptions the patient entered the hospital moribund, with a history and physical examination consistent with long-standing ulcer and acute perforation of thirty-four hours' duration. Operation was not performed and autopsy was unobtainable. The other 3 patients survived without operation, and all the cases fulfilled the following criteria: history compatible with recent perforation; physical signs on admission consistent with peritonitis; free air under the diaphragm demonstrable by roentgenogram; and ulcer shown by a subsequent barium meal.

Only 13 patients, or less than 4 per cent of the entire group, were women. This ratio of 1:25 is interesting, since the sex ratio of ulcer in general is approximately 1:6. In fact, the proportion of women with ulcer who meet with the complication of perforation is somewhat in accordance with the peculiar protection they seem to possess from fatal hemorrhage from ulcer.[2] The incidence of the other chief surgical complication of ulcer—namely, cicatricial obstruction—is more nearly equal in men and women. It has been suggested that gastric ulceration in women is more apt to be benign than it is in men. Although our figures are not large enough to assure us of this fact, we are inclined to believe that it is not true, but that the same suspicion regarding malignancy should be held in both sexes.[3] Six of the female cases of perforation were duodenal and 6 were gastric; 1 patient recovered without operation. Although there were 5 deaths in these 13 cases, the group is so small that we can only surmise that acute perforation of ulcer in women, although much rarer than it is in men, may, when it occurs, be more hazardous.

Considering only the 321 male cases in our series, we can divide them according to location of the ulcer as shown in Table 1. This would seem to indicate that the risk from perforation of an

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ulcer proximal to the pylorus is slightly greater than if it occurs in the duodenum. Although these figures must encompass a definite slight error, owing to the operator's inability to determine invariably the exact location of the ulcer, the ratio of gastric to duodenal in this group is nevertheless comparable to that found in our clinic for other complications of ulcer.[4]

TABLE 1. *Incidence and Mortality according to Location (321 Cases).*

LOCATION	NO. OF CASES	NO. OF DEATHS	MORTALITY %
Duodenum	218	59	27.1
Stomach	70	21	30.0
Jejunum	1	0	0.0
Unspecified	32	3	9.4

Nine patients in the entire group had already survived a previous perforation. Strangely enough, all these recovered from the second episode. It is unlikely that this was merely coincidence; more probably the patient, recognizing a recurrence of his former symptoms, delayed less in obtaining treatment. Doubtless he called attention to his previous condition and made it easier for his physicians to make the diagnosis; thus the all-important time factor was utilized to his advantage.

Often the question arises regarding the proper treatment for the patient who has recovered from acute perforation. How persistently should palliative management be carried out after perforation? Should such a patient be subjected to a radical operation if symptoms persist or if conditions are such that proper self-care is unlikely? The danger of a second perforation has often been raised. It is, of course, impossible to make any blanket rule covering the situation; we do believe, however, that patients recovering from perforation should be carefully followed and the same principles of good ulcer management carried out as in those who have not suffered this complication. If the response to conservative treatment is satisfactory, there is no reason to classify them in a separate category. In fact, such patients are probably no more likely to be invalided by their malady than is the average ulcer patient. If the complication of cicatricial stenosis, massive hemorrhage or intractability does occur, then surgery is justifiable.[5]

There was 1 case in which simultaneous perforation of more than one ulcer apparently occurred. This was unrecognized at operation, and the patient succumbed to peritonitis. Such a possibility is unlikely, and it may reasonably be suspected that the second ulcer perforated during the convalescence following the suture of the first. Certainly there is no way to foresee such a complication, and this incident does not warrant extensive exploration to avoid overlooking a double perforation. The dangers of too much handling of tissues, under these circumstances, far outweigh the risk of overlooking a second perforation.

If our series is divided into its component five-year periods, as shown in Table 2, it is apparent that as early as 1920 the results of treatment became stabilized. It is also obvious, in spite of the elimination of drainage, concomitant gastroenterostomy and so forth, as well as the marked improvement in anesthesia, fluid balance, blood chemistry and other preoperative and postoperative adjuvants, that there has been a striking failure in lowering the mortality rate. Since an increasing number of perforated ulcer patients have been treated in our clinic in the last three five-year periods, with a variation in mortality of less than 0.5 per cent, we have further analyzed this group of 255 patients to see whether any light can be thrown on the problem.

TABLE 2. *Incidence and Mortality according to Five-Year Periods (334 Cases).*

PERIOD	NO. OF CASES	NO. OF DEATHS	MORTALITY %
1916–1920	36	11	30.6
1921–1925	43	11	25.6
1926–1930	90	24	26.7
1931–1935	74	20	26.5
1936–1940	91	24	26.4

In Table 3, we have regrouped these cases according to the season of the year in which they occurred. Thus, it appears that during the winter months the mortality is highest, while during the autumn it is definitely at its lowest point. In an effort to account for this variation, we have plotted in Figure 1 the curves of yearly death rates from acute respiratory-tract infection in Massachusetts and of the mortality rates from perforated peptic ulcer in our clinic. Although these curves are scarcely comparable, it is obvious that they tend to parallel each other, particularly in that no peak in the former curve is without its counterpart in the latter. The sharp drop in both curves in 1940 is doubtless due to the universal use of

TABLE 3. *Incidence and Mortality according to Seasons (255 Cases).*

SEASON	NO. OF CASES	NO. OF DEATHS	MORTALITY %
Winter	59	22	37.3
Spring	64	17	26.8
Summer	56	13	23.2
Autumn	76	16	21.0

sulfonamides. It appears, therefore, that there is some relation between the mortality rate for perforated ulcer in our clinic and the virulence of the current respiratory-tract infection in the community. In support of this hypothesis are the observations of Griswold and Antoncic,[6] DeBakey[7] and Henry[8] that denizens of the respiratory tract are by far the commonest pathogenic organisms cultured from the peritoneal fluid in these cases. Our own bacteriologic studies are in accord with these observers. In 47 cultures reported positive, 38 showed either pneumococcus or streptococcus; 34 per cent of these patients died, while only 7 per cent of those whose peritoneal cultures were reported as negative succumbed after closure of their perforation. It is in this group with positive cultures of virulent organisms that more modern methods of treatment by chemotherapy are apt to be effective. It will be surprising if the next report from our clinic on this subject fails to show a substantial decrease in the mortality rate.

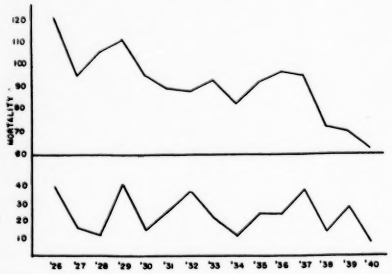

FIGURE 1. *Comparison of Pneumonia Deaths and Operative Mortality in Cases of Perforated Ulcer.*

The upper curve shows the deaths from pneumonia per 100,000 population in Massachusetts; the lower curve shows the corresponding percentage mortality rates in cases of perforated ulcer at the Massachusetts General Hospital.

Diagnosis in our group was rarely difficult. The history of previous indigestion is of importance, but there were a number of perforated ulcers in patients who had never been aware of any digestive disorders. Doubtless a better understanding regarding the so-called "silent" or painless area present in the duodenums of a great many people will lead to prompter diagnosis and treatment in such cases. The suddenness of the onset, with shock producing pain, localized in the epigastrium, should challenge every physician to suspect the diagnosis until disproved. Too often the onset of perforation is confused with gallstone colic, acute indigestion or angina, and the admission of the patient to a hospital is delayed for a dangerous period. In the hospital, moreover, time is often wasted in getting an x-ray examination. That free air within the abdomen can be demonstrated in a large percentage of such cases has been shown in our own series, with an incidence of 72 per cent. This doubtless could be improved on by keeping the patient in an upright position for several minutes prior to the examination or by using the method of Williams and Hartzell,[9] who advise a lateral position for x-ray examination. Our own experience has convinced us that this confirmatory evidence is seldom necessary, and we are certain that much valuable time can be lost by laying undue stress on this method of diagnosis.

Figure 2 indicates diagrammatically the incidence and mortality according to the age of the patient. A comparison with similar data[6, 7] for other series reveals a tendency for our group to contain a larger proportion of older patients. Thus, 35 per cent of our patients had passed their fiftieth birthday, whereas most other series give figures of 18

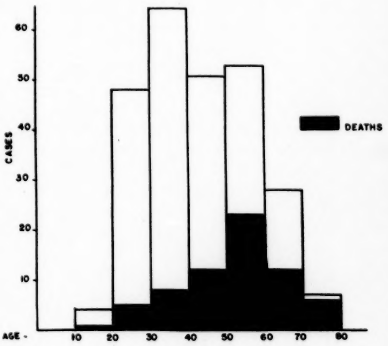

FIGURE 2. *Incidences of Cases and of Deaths according to the Age of the Patient.*

to 23 per cent for this subdivision. Coupled with the consideration that the mortality in these ranges is well over 35 per cent, this fact must play a significant role in the statistics for the group as a whole. Indeed, 70 per cent of all our fatalities were in the older age group. Still further causes for delay in diagnosis are met with in the patients of advanced age, since it is here that the need for excluding coronary occlusion and acute pancreatitis arises in all upper-abdominal disturbances. The time element is so important that exploratory incision under novocain should be made in cases of doubt, in preference to waiting until the diagnosis is clear.

Surgeons unanimously agree that the time interval between perforation and closure outweighs all other factors in influencing the mortality. This interval could be accurately determined in 160 of our cases and is graphically presented in Figure 3. Although at first glance it appears that a

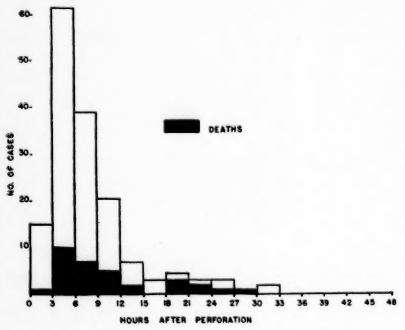

FIGURE 3. *Incidences of Cases and of Deaths according to Elapsed Time between Perforation and Operation.*

gratifying preponderance of patients came to operation within the first twelve hours of their disease, actually the situation is much more urgent than that, for the curve of mortality with respect to elapsed time (Fig. 4) shows its most rapid rise between three and six hours after perforation.

Sixteen patients came to operation between fifteen and thirty-three hours after perforation.

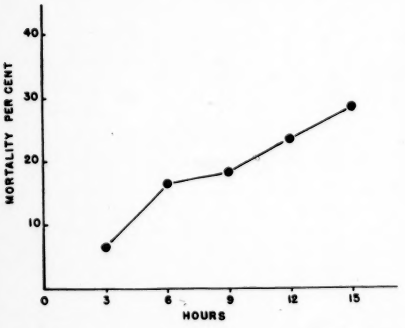

FIGURE 4. *Mortality Rate according to Elapsed Time between Perforation and Operation.*

Nine survived, but it is of interest that those who did so had either chemotherapy (2 cases) or specific mention in the operative note that the perforation was found already sealed off—with one exception, a patient who had a perforation described by the surgeon as "pin-point" in size.

Twenty-five patients not shown in Figure 3 were either not operated on or came to operation forty-eight hours after perforation. Of these, 8 survived, and in all the perforation had already sealed spontaneously, as demonstrated at operation (5 cases) or by the fact that they survived without surgery (3 cases). It is probably not mere chance that no case of ours was subjected to operation between the thirty-third and forty-eighth hours after perforation. It is more reasonable to assume that spontaneous sealing, if it is to occur at all, has most frequently taken effect by twelve to fifteen hours after perforation. Patients who escape surgery until the latter part of the second day will then fall into three categories: those in whom the perforation has sealed and the improvement has been sufficient to warrant conservative treatment; those who have full-blown progressive peritonitis, in whom surgery is out of the question; and those in whom the earlier peritonitis has become localized and obstruction or abscess is developing.

Discussion

Patients suspected of having acute perforation of the stomach or duodenum should be hospitalized at once, and exploration should follow confirmation of the diagnosis with the least possible delay. Acute perforation ranks as an emergency second only to cessation of respiration and massive hemorrhage. A delay of only a few minutes need be expended in passing the indwelling gastric tube and starting intravenous fluid. Roentgenologic and other diagnostic aids should be reserved for those cases in which the findings will influence the decision whether or not to explore. The diagnosis that in the recent past has most frequently caused delay in prompt operative treatment is acute pancreatitis. Diagnostic peritoneal aspiration to determine the character of the free fluid, or even a short exploratory incision under novocain, is undoubtedly a safer and surer method of resolving this difficulty than any amount of observation and supportive treatment.

We agree with Wangensteen[10] that cases seen twelve hours after onset should be examined with particular attention for signs of localization, and evaluated with reference to possible nonoperative treatment—leaning more to this course in the older age group. In the final analysis, surgery has little to offer except mechanical closure of the perforation, and should the patient be fortunate enough for this to have been accomplished spontaneously, his chances of recovery are undoubtedly

better without the added burden of anesthesia and operation. This procedure fails to consider the possibility of leakage at the site of spontaneous closure, an accident occasionally mentioned in the literature. Any estimate on the chances of this complication must await the accumulation of more data than are now at hand. With the patient on constant gastric suction and Ochsner's regimen, however, it appears to us theoretically possible to reduce the incidence of this accident to a minimum.

Anesthesia should be varied according to conditions. Proper use of local or spinal anesthesia may be advantageous. Gastric intubation and suction should precede all anesthesia, particularly if by an inhalation method. At operation, the simplest means of effecting closure is the most desirable one. This may be done by sutures in small perforations or by an omental tab held loosely over the opening as described by Graham.[11] Routine culture of the abdominal fluid should be taken and as much free fluid removed as can be reached with a gently manipulated suction tip, particular attention being paid to the pelvis and subdiaphragmatic spaces. Drainage of the abdominal cavity is contraindicated.

On the basis of the findings of this study, we believe that failure to use any therapeutic agent that has demonstrated its value in the treatment of respiratory-tract infections is a serious omission. Indeed, reports[6] have already appeared describing the use of chemotherapy locally and parenterally in this disease. The postoperative use of sulfonamide compounds may be directed intelligently on the basis of the peritoneal cultures.

Postoperatively, the stomach should be kept on constant aspiration until it is apparent that there is no leakage at the point of closure, also until it is obvious that secretions meet no obstruction in the pylorus or duodenum, and until there is re-establishment of the normal peristaltic function. Parenteral fluids, vitamins, blood or plasma should be administered as indicated. The use of morphine to retain small-bowel tone is essential but should be tempered with wisdom, lest secretions be allowed to collect in the lungs and bronchi. Tracheal aspiration, as described by Haight and Ransom,[12] should be used at once to remove troublesome bronchial exudate that the patient is unable to expectorate.

Summary

Three hundred and thirty-four cases of acute perforation of gastric or duodenal ulcer were seen at the Massachusetts General Hospital in the years 1916 to 1940, inclusive.

The mortality by five-year periods shows no significant change during the past fifteen years.

The mortality during the winter months is appreciably higher than during the other seasons.

There appears to be some relation between this mortality and the virulence of current respiratory-tract infection.

The mortality rises with the patient's age.

The interval between perforation and closure is of fundamental prognostic importance.

In the majority of patients who recovered when more than fifteen hours had elapsed between onset and operation, their perforation had already spontaneously sealed.

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PAROXYSMAL TACHYCARDIA IN PREGNANCY

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THERE has been some disagreement concerning the incidence of paroxysmal tachycardia in obstetric cases, and the true incidence is uncertain. Hamilton and Thompson[1] found it in 13 out of 781 patients with chronic rheumatic heart disease. However, they believe that it is found frequently during pregnancy in women who otherwise have sound hearts. Jensen[2] quotes a number of authors to indicate the conflicting opinions concerning the incidence of this condition. He concludes by saying that 19 cases have been recorded in such a manner as to leave the diagnosis beyond reasonable doubt. Eight of these had valvular disease, while 11 showed no evidence of heart disease. Browning and Clark[3] described 2 more cases and published the electrocardiograms.

The case we are presenting is of special interest because of the apparent five-year duration of the paroxysms of tachycardia, during which time the patient delivered four babies.

CASE REPORT

Mrs. A. H., a 24-year-old white woman, was under observation at the Providence Lying-in Hospital during the latter part of four pregnancies. She had her first child on October 22, 1936, at the age of 19 years, and her last on November 30, 1941. During these pregnancies she was followed for 3 months, 5 months, 3 months and 3 months, respectively. Whenever she was examined throughout these periods she had short runs of tachycardia, interrupted by 1 to 4 slow beats. These findings were consistent with electrocardiograms taken during her first and last pregnancies. Throughout the past 5 years she had neither been conscious of any irregularity of the heart rhythm, nor had she had any discomfort.

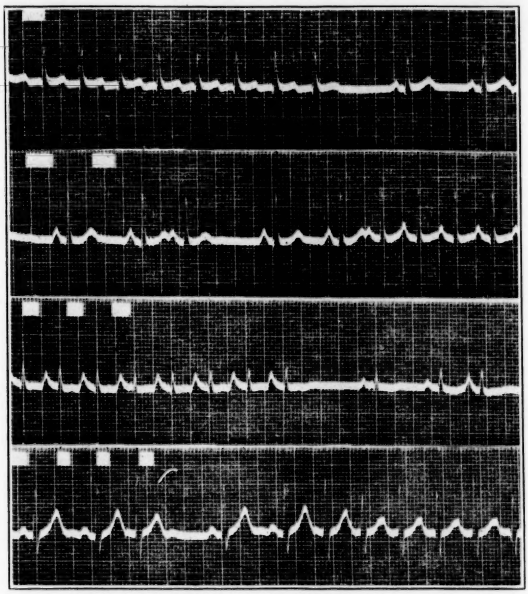

FIGURE 1. *Electrocardiogram Taken Two Months before Delivery.*

The past history was negative except for measles and mumps at the age of 11 years and a tonsillectomy and adenoidectomy for prophylactic reasons at the age of 5.

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In particular, there was no history of rheumatic fever, chorea or sore throat. There had been no symptoms associated with hyperthyroid activity.

Physical examination showed no evidence of heart disease. A Grade 2* systolic murmur, heard during the slow beats and noted at the time of her first admission, persisted. The thyroid gland was not enlarged. The blood pressure ranged during the 5-year period from 110/69 to 122/86.

The usual laboratory findings were normal. The blood Wassermann reaction and urinalysis were negative. An x-ray examination of the heart on January 13, 1942, showed no enlargement. There was slight shifting of the heart due to scoliosis.

The electrocardiograms (Fig. 1) show a very interesting and unusual type of arrhythmia, characterized by short runs of paroxysmal tachycardia. These start with an ectopic beat and have a pause immediately following the spontaneous termination. The first complex following a run of tachycardia presumably represents the normal for the patient. In the record made before delivery, there are no places where more than two normal complexes occur in sequence. More often the slower rhythm is a coupling of a normal beat with an auricular ectopic beat. In the portions of the record showing normal complexes the rate is 64 per minute. The coupling has a rate averaging 94 per minute, and the runs of tachycardia average 140 per minute. There is only a slight variation in rate whenever the tachycardia is present.

For the most part there is very little difference in the PR interval time regardless of the type of P wave. It is evident in some of the tracings, particularly in Lead 1, that the last complex in the runs of tachycardia has a different shape of P wave than have the immediately preceding complexes. It seems that a shift in the origin of the impulse breaks up the run of tachycardia. This point is evident in some of the other leads, but to a lesser degree.

In the electrocardiograms made 6 weeks after the last delivery (Fig. 2) there are no runs of tachycardia. The arrhythmia is due to ectopic beats that vary considerably

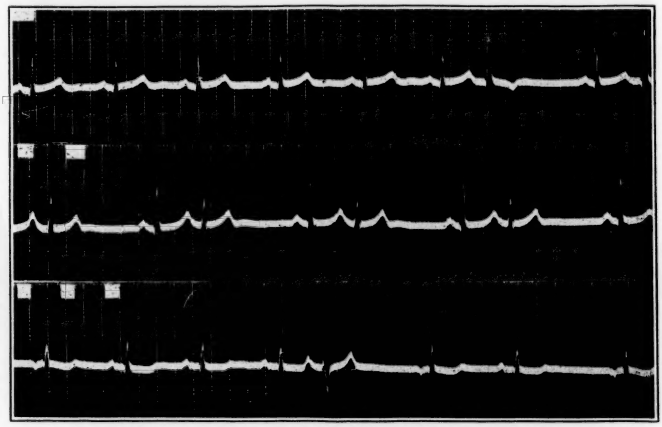

FIGURE 2. *Electrocardiogram Taken Six Weeks after Delivery. Note the ectopic beats in Lead 3.*

in the point of origin. Some of these beats are definitely auricular, apparently arising near the sinoauricular node. Others are of a very different pattern, and are followed by ventricular complexes wholly unlike the normal. Lead 3 best illustrates this point. Some of the P waves are inverted, showing almost no change in the PR time as compared with the normal. These complexes have a ventricular response exactly like the normal. Other P waves are high and pointed, followed by ventricular complexes of a pattern usually associated with those arising in the ventricle. These odd complexes show a PR time that is within normal limits and almost identical with that of the normal beats. The ventricular response obviously does not follow the normal sequence.

This unusual irregularity of heart action known to have been present in this patient since her first pregnancy in 1936 has in no way interfered with her normal activity.

Attempts to control the tachycardia were unsuccessful. Small doses of digitalis were given during the last few weeks of the third pregnancy, without any effect. During the last pregnancy the patient was well digitalized, without any change in the rate or rhythm of the heart. After delivery she was given 3 gr. of quinidine sulfate† every 2 hours for thirteen doses. This was stopped because she complained of nausea. The electrocardiograms taken after the last dose showed a change in the pattern of the ectopic beats, with more coupling of normal and ectopic beats followed by longer runs of auricular tachycardia. The pa-

*Classification — Grades 1 to 6, according to loudness.

†Quinidine sulfate was considered during pregnancy but was not used until after delivery because we did not know its action on the uterus. There seems to be some reason for believing that the drug acts on the uterus only during labor. Browning and Clark[2] employed it during pregnancy and quote some authors recommending its use.

tient was discharged from the hospital on 3 gr. of quinidine sulfate three times a day, but neglected to take it.

Summary

A case of paroxysmal auricular tachycardia seen throughout the latter part of four pregnancies over a five-year period is reported.

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GOVERNOR'S ADDRESS*

Robert O. Blood, M.D.†

Concord, New Hampshire

WE ARE met here tonight at a time when more people are being maimed in the world than at any other period in its history. We had a world war once that we now call World War I, but that was only a dress rehearsal for the present conflict.

Men in the medical profession have a greater job to do the world over than has ever befallen any generation of medical practitioners in our time or in the world's history. I am sure that physicians will find themselves equal to this task, as they have in all their trials in the past years of civilized history.

We here in this state have a real job to do, and in my dual capacity — practicing medicine and at the same time being the chief executive charged by the people with the administration of the state business as a whole — perhaps I feel a little greater responsibility because of my medical background and training as it relates to medical care than a layman would in my position.

We, the State, are spending a tremendous amount of money in medical care, both as it relates to prevention and control of disease and to the care of those who are diseased. Last year we spent almost $1,300,000 for other than the institutional care of patients. For cancer patients the State spent the sum of $43,000, and the total expended by the Cancer Commission was over $58,000. The State Hospital spent the sum of $866,000 last year for the care of patients. And I may say that Dr. Dolloff, your retiring president, is running an excellent institution and that the patients are well cared for; also, the State is in a better position by having them segregated there than it would be if they were scattered about. Over 2300 patients are there now, and it is hard to predict where the care of those with mental diseases will end. The situation is a little more hopeful as it relates to tuberculosis, where we are one of the lowest nine states in deaths per 100,000 in a year. Our rate has gone constantly down for the last twenty-odd years. However, we still annually spend the sum of $175,000 for the care of patients in the institutions at Glencliff and Pembroke.

If you add together all the sums I have mentioned, you will see that for the care of people in institutions, for medical care as it relates to prevention, control and so forth, we are spending a very considerable amount of money.

I believe that the medical profession is somewhat derelict in its duty in not contributing more in personnel to the legislative halls of this and other states. You have no right, unless you participate actively in the control of the legislation that is passed, to expect a layman to do too good a job. So may I leave an appeal that some of you who can go to the Legislature do so and lend a little medical influence there? It isn't a very hard job.

I want to pay my respects to the medical legislation that you have received from our legislature. I believe — and I think you will agree with me if you look over the laws as they relate to medical care, sanitary regulations and so forth — that this state will rank high among the states of the country. Changes continue to be necessary. Public-health and the Board of Health activities have grown so rapidly that changes are always necessary. I told you last year that the original law, passed in 1887, said that there never should be in any one year expended for health activities more than $3000. But from that period we have grown, slowly at first, but recently very rapidly, and the result is what you would expect it to be; we have added function after function to our health activities, and we have never "sugared them off." Revamping is as necessary in the State's business as it is in any other business where you add functions, one on top of another.

The medical profession might well consider learning something about our state institutions —

*An address delivered at the annual banquet of the New Hampshire Medical Society, Manchester, May 13, 1942.

†Governor of New Hampshire.

where our people who are physically and mentally ill are housed — by visiting these institutions once in a while and seeing what is being done. I think it would surprise you if you asked the men here how many of them had visited Glencliff, Pembroke, the Laconia School and the State Hospital.

We also have a large responsibility in molding public opinion. You men have been privileged — or you could not be practicing medicine — to obtain a college education. You are marked men because of your training, and because of that, you have increased obligations with the privileges and training that you have received. There never has been a time in this state when we needed more for purposes of morale, and for purposes of assistance in many ways, leadership like the leadership that you men can give in your communities.

The federal government is, of necessity, — and, we hope, wisely, — making regulations that affect every one of us. So long as those regulations are there, and so long as those regulations are fair to all of us, no one in this state will hesitate to carry on as he should.

In this war, you and I and every last one of us have a job to do, and we will contribute, we must contribute, cost what it will, — you and I in this state and the people the world over in the United Nations will contribute, — all that is necessary to defeat the Axis; for much as it costs, it will cost much less to win a war than to lose one.

MEDICAL PROGRESS

PHARMACOLOGY AND PHARMACOTHERAPY*

HARRY B. FRIEDGOOD, M.D.†

BOSTON

IN RECOUNTING strategic advances in any branch of medicine, one must take into consideration not only the new discoveries of importance, but also the welfare and aims of the field in general. Both of these depend heavily on the stimulus and guidance of men of vision who reaffirm established principles, discover new ones and adapt all of them to the ever-changing conditions of each succeeding era. Pharmacology is a science that is traditionally devoted to the study of drugs and their effects on the animal organism; but the responsibilities and interests of the pharmacologist do not end there. His ultimate concern is with the therapeutic application of the drugs whose effects he observes experimentally. Although this viewpoint enjoys universal recognition, it has not always been possible to accomplish its aim, principally because there has been altogether too infrequent professional collaboration between pharmacologist and clinician. Fortunately, there have been an increasing number of such arrangements in more recent years. In the recent passing of Dr. Soma Weiss, pharmacology has lost the genius of an internist who saw the problem of pharmacotherapy in its broadest aspects, and who contributed to it in an outstanding fashion.

Modern trends in the development of medicine leave no doubt that the field of the pharmacologist includes not only a limited study of the effects of drugs, but encompasses also an increasingly large area of the neighboring sciences of bacteriology, immunology, physiology, histoanatomy and so forth. This review, although limited in its scope, pays tribute to this important conception by including references to representative investigations in some of these fields, which meet on the common ground of pharmacotherapy.

CHEMOTHERAPY

It is scarcely possible to exaggerate the importance of the continuing advances in chemotherapy. The spotlight of interest previously monopolized by the sulfonamides is being shared more recently with reports of the bactericidal activity of gramicidin and penicillin, and with further observations on massive-dose drug therapy in early syphilis. So far as the sulfonamides are concerned, a survey of the past year's publications indicates that the topics of major interest are as follows: mode of action; use in local therapy of burns, penetrating wounds of joints, compound fractures, ophthalmologic conditions (trachoma) and cutaneous infections; prophylactic implantation of sulfanilamide in clean operative wounds; and new derivatives, principally sulfasuxidine.

Kohn and Harris[1, 2] have studied quantitatively the growth and respiration of *Escherichia coli* in

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, Vol. III, 1942* (Springfield, Illinois: Charles C Thomas Company, 1942. $5.00).

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different mediums in the presence and absence of the sulfonamides. At the bacteriostatically active concentrations studied, the sulfonamides do not inhibit respiration of the resting or growing organism. Kohn and Harris conclude that certain substances essential to growth and multiplication are stored in the cell, and that the rate of their synthesis is inhibited by sulfonamides.

Richardson[3] has investigated the small Heinz bodies, which appear within twenty-four hours after the beginning of sulfanilamide therapy in the majority of mature red blood cells. He has found that these increase in size until they reach their largest diameter by the fourth or fifth day, when blood destruction is at its peak. The occurrence of these bodies is independent of the presence or absence of changed pigment, and preliminary analyses show that they are made up of considerable amounts of cholesterol and protein and very little iron.

The idea of employing sulfonamides in the treatment of local infections and for prophylactic purposes in surgery logically follows in the wake of its successful use in systemic infections, and represents one of the major recent achievements in this field. Hooker and Lam[4] report the successful local use of sulfanilamide powder in extensive burns, which healed rapidly and uneventfully. They were particularly impressed by the rapidity of absorption of the powder from the burned surfaces and the high blood levels that were consequently induced. Key and Burford,[5] Long and Dees[6] and Bickford[7] found sulfanilamide powder highly effective in the prevention of infections in compound fractures, crushing and lacerated wounds and penetrating wounds of joints. Key and Burford[8] and Long and Dees[6] emphasize the prophylactic value of sulfanilamide powder locally in clean operative wounds[8] and in any gastrointestinal surgery with soiling of the peritoneum.[6]

Keeney, Pembroke, Chatard and Ziegler[9] advocate the use of a 5 per cent sulfathiazole ointment in the treatment of cutaneous infections on the basis of a study in 69 patients with infected infantile and adult eczema, seborrheic dermatitis, impetigo, acne vulgaris, bacterial folliculitis and furunculosis. Toxic effects were not observed.

Cosgrove and Hundley[10] have continued the studies of Loe,[11] who first reported the successful treatment of trachoma with sulfanilamide. They too are impressed with the efficacy of local therapy, and report the cure of 83 per cent of patients in the first and second stages of trachoma.[12] They also found such local therapy efficacious in gonorrheal ophthalmia, pneumococcal conjunctivitis and posttraumatic corneal ulcers.

Most recently studied of the newer sulfonamide derivatives is succinyl sulfathiazole (sulfasuxidine). It was synthesized by Miller, Rock and Moore[13] and subsequently studied clinically by Poth and Knotts[14] and Mattis and Welch.[15] Succinyl sulfathiazole exerts marked enteral bacteriostatic action, and the indications are that it will prove successful where sulfaguanidine has fallen short of its early promise. Pharmacologic studies in dogs and monkeys show that succinyl sulfathiazole administered orally has little toxicity and that it is poorly absorbed from the intestinal tract, so that only an average of 4 to 5 per cent of the ingested drug is excreted by the kidneys. Its action is essentially in the intestinal tract, as demonstrated by the reduction in the count of *E. coli* and the marked inhibition of anaerobic proteolytic bacteria, which causes the feces to become relatively odorless. Preliminary observations indicate that the dysentery bacilli, including the Shiga, Flexner and Sonne strains, are susceptible to its bactericidal action. This drug also promises to reduce greatly the hazards of intestinal surgery.

Dubos[16] has opened a second front in man's fight against bacterial infection by starting with the conception that one can find in nature microorganisms selectively adapted to the decomposition of almost every conceivable type of organic compound. He points out that like all living cells, micro-organisms carry out their biochemical functions by means of enzymes and catalysts, which can often be extracted in an active form from the bacterial cells that produce them. These catalysts show a remarkable specificity with reference to the type of reaction that they can bring about. With these considerations in mind, Dubos isolated from soil various new bacterial species that produce specific catalysts selectively adapted to protect experimental animals against certain bacterial infections. One of these agents (polysaccharidase), which is neither bacteriolytic nor bactericidal, acts by destroying the protective capsular material of pneumococci and thus renders them susceptible to the phagocytic action of the cells of the infected host. Dubos extracted the other protective agent, gramicidin, from a sporulating soil bacillus. Unlike the polysaccharidases, it does not belong to the class of enzymes, but must be regarded as a true antiseptic, minute concentrations of which inhibit the growth of susceptible species in nutrient mediums (bacteriostatic action), whereas higher concentrations actually kill bacteria (bactericidal effect). Gramicidin appears to interfere with some essential metabolic function of the invading microorganisms. In this respect, the mechanism of its protective action presents some analogy with that of the sulfonamides. The bactericidal action of

gramicidin is in some way related to the staining characteristics of the bacterial cells. It does not affect gram-negative bacilli, and its action is apparently tied in with some as yet unidentified structural difference between gram-positive and negative cells. Dubos believes that it is not too much to hope that micro-organisms capable of attacking other types of pathogens or their toxic principles will eventually be discovered in nature.

In their experimental and clinical studies on gramicidin, Herrell and Heilman[17] have observed that this substance has a powerful hemolytic effect, which renders its systemic use inadvisable. They recommend that it be used locally or in irrigating infected cavities that do not communicate with the blood stream. They used thyrothricin (the crude substance from which gramicidin is recovered) locally in the treatment of 12 cases of various types of infection with gram-positive bacteria and observed marked beneficial results in most cases without demonstrable damaging effects to the host's tissues.

The preparation of penicillin, an extract of a mold, opens a new and exciting chapter in the history of chemotherapy. An evaluation of the earliest reports on penicillin suggests that, if anything, it may have wider clinical application than gramicidin. Preliminary studies indicate that it can be given intravenously with impunity and that its use in the form of strong solutions is innocuous to tissue cells. Its bacteriostatic action in vitro resembles that of the sulfonamide drugs, with the following differences: the bacteriostatic action of penicillin against streptococci and staphylococci is much greater; the action of penicillin on these organisms, unlike that of the sulfonamides, is influenced to only a minor extent by the number of bacteria present; and in suppurating wounds, the bacteriostatic power of penicillin against these organisms, contrary to the sulfonamides, is not antagonized by hydrolytic protein breakdown products or products of tissue autolysis or pus.

The clinical experiments with penicillin are encouraging thus far, according to the report of Abraham and his co-workers.[18] They administered penicillin intravenously to 6 patients with staphylococcal and streptococcal infections that had failed to respond to all previous therapy including the sulfonamides. Penicillin induced a fall in temperature and resulted in improvement of the local and general condition. The future appears to hold much that is good in store for gramicidin and penicillin and other substances of similar origin, not only from a chemotherapeutic viewpoint, but also because investigations that deal with the latter are bound to turn up collateral observations which should throw light on obscure phases of cellular metabolism, enzyme chemistry, immunology and bacteriology.

Extensive studies on massive-dose therapy of early syphilis have been in progress for several years by virtue of a laudable co-operative experiment carried out under carefully controlled conditions in a number of widely separated hospitals. It was Ehrlich who first attempted to cure syphilis with massive doses of arsphenamine, but he abandoned the method because of unsatisfactory results. Chargin, Leifer and Hyman reintroduced the massive-dose procedure in the form of a slow intravenous drip with neoarsphenamine. The frequency of untoward reactions (especially peripheral neuritis) led them to substitute an arsenoxide, Mapharsen, for neoarsphenamine. Leifer, Chargin and Hyman[19] report that 81 per cent of 334 patients with early syphilis were cured in five days by this method of treatment, and Elliott, Baehr, Shaffer, Usher and Lough[20] similarly found that 85 per cent of their patients in their series of 1600 cases were cured with identical therapy (1200 mg. of Mapharsen is the optimal total dose). Both groups of investigators encountered toxic encephalitis, which was a fatal complication in 0.3 per cent of the cases reported by Elliott et al. and caused cerebral symptoms without death in 1.1 per cent of the patients studied by Leifer et al. Encountered also were slight nausea, vomiting and diarrhea, which disappeared with the establishment of tolerance to the drug. Elliott and his co-workers found little evidence of liver damage and no renal damage, dermatitis exfoliativa, blood dyscrasias or nitritoid reactions in their 1600 treated cases. Although the results of these investigators are most promising, it would seem to be the better part of wisdom not to release their technic to the general practitioner until more work is done under controlled conditions with particular reference to the toxic arsenical encephalitis.

Cardiorenal Drugs

The bioassay of digitalis is a perennial problem in pharmacology. This past year has been no exception in this regard. Gold, Cattell, Kwit and Kramer[21] point out that contrary to general expectation, current official methods for the standardization of digitalis do not ensure uniform potency of the drug, because the *U.S.P.* frog method of assay is not applicable to the human being. Their experiments show that when the frog and cat methods give different values for the potency of a preparation, the figure obtained by the cat method applies to human beings, whereas that obtained by the frog method does not. They have found, furthermore, that specimens that deteriorate in po-

tency with aging, as judged by the frog method, are not found similarly wanting either by the cat method or on clinical trial in human beings. More recently they[22] have described a method of assay by means of which the potency of digitalis preparations can be compared in human beings, using one and the same subject and thereby eliminating errors arising from individual differences in susceptibility. Batterman, Holman and DeGraff[23] differ with Gold and his co-workers on the value of the cat method. They have studied preparations that were identical in potency according to the cat method, but weaker or stronger so far as the desired clinical therapeutic effects were concerned. They suggest the use of a mixture of constant proportions of three crystalline glycosides (lanatosides A, B and C) isolated by Stoll and Kreis from *Digitalis lanata*. None of the three satisfies the criteria for an ideal digitalis preparation, but their correct combination results in a product of known chemical composition, which they believe compares favorably in its clinical effect with *D. purpurea*. This preparation is assayed by the gravimetric method, which reinsures greater accuracy and uniformity of dosage.

A new diuretic worthy of clinical consideration, judging from preliminary observations, is the mercurated allyl succinylurea with theophylline recently reported by Nuhfer, Mellish and Buchter.[24] The toxicity of this solution was compared with that of Salyrgan theophylline. Ninety per cent of the dogs that were given 10 mg. of mercury per kilogram in the form of the new diuretic survived, whereas the Salyrgan preparation was fatal to 90 per cent of the dogs treated with a corresponding dose of mercury. Neither drug affected the cardiac automaticity, nor did a serious change in blood pressure result from the administration of 5.32 mg. of mercury per kilogram. A marked diuretic response was elicited in dogs by the preparation of mercurated allyl succinylurea with theophylline. Preliminary studies with this preparation at the Peter Bent Brigham Hospital show that an excellent diuresis can be induced in edematous cardiac patients without evidence of toxicity.

Blood Anticoagulants

The problems concerned with the treatment of thrombosis and the prophylactic therapy against postoperative thrombosis have been in the foreground of pharmacotherapy for some time. Heparin was naturally the first substance to be used in studies of this type. Many papers dealing with this subject have appeared during the past year or so, and for the most part the results indicate that heparin has a place in the treatment of thrombosis and in the prophylactic care of the postoperative condition. Its probable value in embolectomy and other kinds of blood-vessel surgery is apparently even greater (Lam,[25] Bauer,[26] Murray,[27] Rea,[28] Ravdin and Wood[29] and Crafoord and Jorpes[30]). An extensive review of the development of this field can be found in an article by Jorpes.[31] Heparin has disadvantages, however, that limit its clinical usefulness; for example, it is expensive, it is effective only when administered parenterally, and its activity is of relatively brief duration. A series of well-conceived, brilliant experiments by Campbell, Roberts, Smith, Link and Overman[32-34] were instrumental in bringing to light a new anticoagulant,— 3, 3′-methylenebis (4-hydroxycoumarin),— which prolongs coagulation and prothrombin time. Their work was based on a previously recognized hemorrhagic disease in cattle (sweet-clover disease), which was described independently by Schofield[35] and Roderick.[36] The isolation and crystallization of the hemorrhagic agent were finally accomplished last year by Campbell, Link, Stahmann and Huebner.[37-39] Recent preliminary communications on the clinical application of the aforementioned discoveries by Meyer, Bingham and Axelrod[40] and Butt, Allen and Bollman[41] give one the impression that this principle bids fair to replace heparin for most purposes. Obviously, a great deal of clinical experimentation under carefully controlled conditions must still be done in order to substantiate the early promise of this substance and the absence of toxicity. The work thus far indicates, however, that the preparation is nontoxic; it is effective when administered orally; furthermore, it has a longer action and is cheaper than heparin.

Narcotic Problem

The narcotic problem has come in for its share of attention during the past year. Demerol, a new analgesic drug, has been studied for its properties of addiction, tolerance and clinical effectiveness with special reference to the possibility of substituting it for morphine. Himmelsbach[42] found that the abstinence syndrome and withdrawal symptoms were typical of, but less severe than, those induced by morphine when Demerol was given to a group of post-addicts or "recovered" patients under controlled conditions. Andrews[43] has observed that the pain-threshold-raising effect of Demerol, as determined by the Hardy-Wolff method, is consistently reduced, and that tolerance to this drug is similar to, but less permanent than, that developed to morphine. Batterman[44] states that Demerol has proved to be a satisfactory and safe drug in over 800 patients, most of whom would have required morphine for the relief of pain.

Slaughter, Parsons and Munal[45] have observed that prostigmin potentiates the pain-relieving action of morphine. Their observation had its origin in the work of Slaughter and Gross,[46] who found that the two drugs were synergistic in their action on the intact dog's intestine and were strikingly similar in some of their cholinergic effects. Their work shows that ⅛ gr. of morphine sulfate plus 1 cc. of prostigmin methyl sulfate (1:2000 solution) acts more rapidly and is more effective than ¼ gr. of morphine sulfate alone. Furthermore, the combination affords excellent preoperative and postoperative sedation and a decreased incidence of postoperative distention and urinary retention.

Dilantin Sodium in Epilepsy and Asthma

An important contribution to the treatment of epilepsy (and possibly bronchial asthma) is to be found in Dilantin Sodium.[47–49] This is a drug which, with little or no hypnotic effect, prevents or greatly decreases the frequency and severity of convulsive seizures in a majority of epileptics. It is said to be much more effective in the management of seizures of the psychomotor-equivalent variety than phenobarbital or bromides. Dilantin is not recommended for patients whose seizures occur only at long intervals, unless moderate doses of phenobarbital are ineffective or induce undesirable side reactions. The great majority of toxic reactions to Dilantin Sodium occur only when large doses are employed. The gastrointestinal symptoms are chiefly nausea and vomiting, while the central-nervous-system toxicity consists of nervousness, tremor of the hands, drowsiness, headache, and ataxia. Hypertrophy of the gums and a toxic dermatitis, varying from erythema to a severe morbilliform rash, are among other toxic effects observed. Another of the toxic manifestations to which attention is being directed is the rapid and progressive fall in the blood ascorbic acid level.[48] This factor has immediate clinical importance from several viewpoints, and awaits further elucidation and evaluation. Shulman[50] has used Dilantin Sodium in bronchial asthma with encouraging results. He was stimulated to try this drug in 7 young children because of the psychosomatic aspects of the so-called "asthmatic personality."

Belladonna and Syntropan

A controversy over the relative merits of *U.S.P.* and Bulgarian belladonna root seems to have been settled satisfactorily. A number of investigations were stimulated by the observations of Raeff, who claimed a distinct measure of superiority for the Bulgarian belladonna plant over others in the treatment of the distressing symptoms of postencephalitic Parkinson's syndrome. Neither Price and Merritt[51] nor Fabing and Zeligs[52] were able to confirm Raeff's work, although the latter believe that a white-wine extract of *U.S.P* belladonna in desiccated form (that is, pressed into tablets) is preferable to the ordinary tincture because the latter is chemically unstable and subject to deterioration.

Obstetricians will be much interested in the observations of Stoll,[53] who has reported that Syntropan reduces the length of labor by half if it is given when dilatation of the cervix begins. It appears to be a safe and effective method for the shortening of labor, although the pharmacologic and physiologic aspects of its effects are still unknown. Stoll believes that its effect may be related to the drug's relaxing action on the lower uterine segment or cervix.

Lipotropic Substances

According to Best, Huntsman and Ridout,[54] a lipotropic substance is one that decreases the rate of deposition and accelerates the rate of removal of liver fat. The study of these substances had fallen almost entirely within the domain of the laboratory scientist until quite recently, when Dragstedt[55] brought it to the attention of clinicians. A number of lipotropic substances have already received careful study, including choline and betaine, methionine and cystine and inositol and lipocaic. From a clinical viewpoint, Dragstedt's studies of lipocaic render it of more immediate interest than any of the other lipotropic substances. The foundations for the interesting discoveries that have been made in this field were laid in 1924 by Allan, Bowie, Macleod and Robinson.[56] They reported that depancreatized dogs receiving adequate amounts of insulin and maintained on a diet of lean meat, sucrose and bone ash did not survive for periods longer than a few months. They also found that the addition of raw pancreas to the basal diet prevented the symptoms of failure of liver function that were due to fatty infiltration of the liver. They suggested, therefore, that the pancreas might produce an internal secretion necessary for the physiologic integrity of the liver. Somewhat later it was demonstrated that egg-yolk lecithin and choline (the active agent in lecithin) could prevent the accumulation of liver fat (Best, Hershey and Huntsman[57]); and Best and Huntsman[58] also found that choline could restore to a normal fat content livers of rats that had been made fatty by a high fat diet. There is considerable controversy concerning the chemical nature of lipocaic and its relation to choline and inositol. For present purposes it is sufficient to point out that lipocaic may play an important role in diabetes mellitus and arteriosclerosis. Dragstedt[58] has pointed out that two types of fatty infiltration

of the liver occur in both diabetes mellitus and experimental pancreatic diabetes. One type is due to poor control of the diabetes by inadequate insulin therapy and is characterized by a normal or high concentration of the blood lipids and acidosis; it is relieved by proper insulin therapy. The second type is due to lipocaic deficiency and is characterized by a low concentration of the blood lipids, impaired liver function, decreased glucose tolerance and insulin sensitivity; it is relieved by lipocaic, but not by insulin. Lipocaic apparently prevents arteriosclerosis in depancreatized dogs, in which there is a greater incidence of this condition than is normal for this species. The implications of these studies are obvious when one recalls that diabetic patients are much more likely to develop presenile arteriosclerosis (coronary disease and peripheral arteriosclerosis with gangrene of the extremities) and that enlargement of the liver due to extensive fatty infiltration is not uncommon in human diabetes mellitus, particularly in children.

Nutritional Achromotrichia

The field of vitamin therapy is too large to be included in a limited review of this type. One vitamin substance, however, which has been the subject of nation-wide publicity, merits a few words in passing. Ansbacher's[59] observations on the chromotrichial actions of *p*-aminobenzoic acid precipitated a controversy as to the nature of the gray-hair factor or factors. Unna, Richards and Sampson[60] and Emerson[61] were unable to attribute chromotrichial activity to *p*-aminobenzoic acid and held that pantothenic acid was the most likely source of this action. Such wide discrepancies suggested that some factor, unrecognized by either group, might be complicating the situation. With this in mind, Martin[62] set up a series of well-controlled dietary experiments on rats in which he found that six basic vitamin factors (B_1, B_2, B_6, choline, calcium pantothenate and nicotinic acid) are adequate for seemingly normal nutrition unless either *p*-aminobenzoic acid or inositol is added to the diet. He found that the addition of one of these two vitamins to the basic diet precipitated a deficiency of the other. He concluded, therefore, that the *p*-aminobenzoic acid deficiency noted by Ansbacher[59] and Martin and Ansbacher[63] was made possible by the inositol that was included in their basic diets. Neither Unna et al.[60] nor Emerson[61] had inositol in their basic diets, which accounts for the fact that they did not encounter a similar deficiency syndrome. Martin attributes this interdependence of vitamin substances to their effect on the bacterial growth in the gastrointestinal tract and hence on the bacterial synthesis of vitamin factors. Experiments such as Martin's serve to re-emphasize the complexity of the biochemistry and physiology of the vitamins. The study of these essential substances from a pharmacotherapeutic viewpoint is still more difficult because clinical experiments are less easily controlled than laboratory conditions. Martin's observations, which dovetail neatly with the experiences of other investigators, suggest that apparently innocuous chemical substances, such as vitamins, may in some circumstances induce undesirable repercussions in the body economy by upsetting what would otherwise be a biologic system in equilibrium. With this in mind, the administration of vitamin therapy to patients who show marked nutritional deficiencies should be approached with more caution than is customary; otherwise the injection or ingestion of large quantities of one or more vitamins can precipitate unrecognized subclinical deficiencies into major problems, to the great detriment of the patient. For these reasons, initial dosages are best kept within the physiologic range, and changes in metabolism should be induced gradually, not abruptly.

Martin's experiments and the experiences of other investigators indicate that there are various patterns of nutritional achromotrichia that are in some way related to the kind of vitamin deficiency that is present. This, coupled with the fact that the chromotrichial action of *p*-aminobenzoic acid is not based on simple biochemical and physiologic reactions, should put the clinician on guard against premature dogmatic conclusions with reference to any phase of this subject. In this reviewer's limited experience, there have been a few patients in whom *p*-aminobenzoic acid has shown chromotrichial activity under special circumstances; but there was also a case in which a combination of estrogen and progesterone restored prematurely gray hair of a lustrous silvery sheen to its original light brown color after several months of treatment. In this connection, the claims of Sieve[64] would seem injudicious, to say the least. With a minimum of published data, Sieve has credited *p*-aminobenzoic acid with a group of unique properties as a result of studying 800 patients in eight months. He states that this vitamin is clinically useful in a number of ways, among which are the following: it darkens gray hair; it intensifies the normal pigmentation of the nipples and mucous membranes of the mouth, vagina and anus; it eradicates areas of vitiligo; it induces a return of color and "changes the hypertrophy" of areas of leukoplakia in the mouth; it causes a decrease or almost complete disappearance of hyperpigmentation of nevi and freckles; it stimulates the libido; it re-establishes the menstrual cycle in amenorrhea

and increases the amount of flow in oligomenorrhea; it cures female sterility (12 out of 22 cases); it benefits asthmatic patients in certain instances; and it increases the appetite and induces a feeling of well-being. Although experimental laboratory evidence indicates that *p*-aminobenzoic acid is biologically active, the list of attributes that Sieve has ascribed to this chemical substance is formidable.

Endocrine Pharmacotherapy

Specific knowledge concerning the biochemistry and physiology of the male sex hormones is of comparatively recent date. Testosterone was synthesized in 1935 by Ruzicka et al.[65] and by Butenandt and Hanisch.[66] In 1936 it was reported that organic acid esters of testosterone, such as the propionate, were more active than testosterone. The most recent advance in this field has been the development of an orally effective androgen in the form of methyl testosterone.[67, 68]

The androgens have become increasingly important in endocrine pharmacotherapy as a result of the availability of synthetically prepared organic acid esters of testosterone. A survey of the literature discloses that there are essentially three types of male sex hormone deficiency that have been treated successfully with these synthetic androgens: hypogonadism — this group includes castrates, eunuchs, eunuchoid individuals and others who exhibit only mild symptoms of androgenic deficiency; the male climacteric syndrome; and cryptorchid prepuberal boys.

There is a unanimity of opinion in the reports of investigators who have used testosterone propionate (parenteral) and methyl testosterone (oral) in the treatment of various types and degrees of hypogonadism. Vest and Howard[69] have reported on the effects of male sex hormone therapy in several hypogonadal men. Libido was restored to 3 of the 4 men who had emissions for the first time. In all 4 cases, the testes increased in size and all symptoms of hypogonadism were ameliorated. Miller, Hubert and Hamilton[70] treated 6 impotent patients under controlled conditions (2 castrates, 2 hypogonads and 2 patients in whom impotence was probably of psychic origin). The castrates regained normal potency and personality disorders appeared to be improved in the others. Among the 54 patients treated by Turner[71] were cases of hypogonadism that responded to androgen therapy with an increase in the hair growth, the penile growth, the libido and the frequency of erections and emissions. The doses of testosterone propionate used by various investigators have ranged from 15 to 150 mg. per week. Byron and Katzen,[72] Kearns,[73] McCullagh,[74] McCullagh and Rossmiller,[75] Foss,[76] Eidelsberg and Madoff,[77] Escamilla and Lisser,[78] and Wilhelm[79] observed that methyl testosterone, orally administered, is highly efficacious in the treatment of the castration syndrome and severe or moderate instances of eunuchoidism. Simonson, Kearns and Enzer[80] have made special notes on the beneficial effects of androgen therapy on the fatigue of eunuchoids and castrates. The reports from various sources cited above state that the dose of orally administered methyl testosterone is from two to six times that of testosterone propionate if one is to achieve comparable results. It has been stated that the severity of the symptoms may determine in large part the dose necessary to control the syndrome. However, it has been the experience of this reviewer, in keeping with that of Kearns,[73] that the more outspoken the condition, the less androgen it takes to control it and the quicker amelioration of the hypogonadism occurs.

With but few exceptions there is apparently little realization of the potential value of the synthetic androgens in the treatment of the distressing symptoms of the male climacteric. This is due mainly to the attitude of a good many physicians who have been reluctant to recognize that the male climacteric is a clinical entity. A recent editorial in the *Journal of the American Medical Association* is an official expression of this skeptical viewpoint.[81] Opinions to the contrary notwithstanding, there is increasing clinical evidence of a syndrome that one may properly term the "male climacteric." The condition occurs spontaneously in men, most frequently after their fortieth year, and yields satisfactorily to androgen therapy if it is properly administered. This reviewer's experience, as yet unpublished, confirms the observations of others who have described this syndrome. The latter is characterized by a lack of mental, physical and sexual drive, and may not include significant impotence in the early stages. The varied symptoms of this condition are headache, emotional instability, a tendency to periods of depression, abnormal fatigue and lassitude, impairment of memory and inability to concentrate, insomnia and occasional symptoms of vasomotor instability. It has been a not uncommon experience to find that individuals suffering from this condition go from one physician's office to another because of what appear to be intangible complaints for which an organic basis cannot be found. They finally become tagged with descriptive symptomatic diagnoses such as psychoneurosis, hypochondriasis, headache of unknown origin and even involutional melancholia.

The literature on this subject is still relatively limited. Schmitz[82] treated 45 cases of the male

climacteric and of impotence and noted improvement in 36 of them; Donald,[83] who reported on a series of 50 cases of the male climacteric, found that the psychologic symptoms improved first and that there was a subsequent return of mental and physical vigor. Venzmer,[84] Monetti,[85] Wolbarst,[86] Kearns[73] and Finkler and Cohn[87] have observed a fairly large series of patients who were treated with either parenteral or oral androgenic therapy. They observed considerable improvement (loss of impotence, re-establishment of mental and physical energy, relief from headache and vertigo and so forth). The dosage of androgen used in the treatment of these patients varied considerably (from 15 to 150 mg. of testosterone propionate per week). In this reviewer's experience, an adequate dosage has been 25 mg. of testosterone propionate parenterally four times per week for four to six weeks, and 30 to 40 mg. of methyl testosterone* orally daily thereafter. For the time being, the only diagnostic procedure is to keep the possibility in mind when a likely case is encountered and to subject the patient to a therapeutic test.

The use of testosterone esters in the treatment of cryptorchidism or infantile genitalia in boys of the Fröhlich type constitutes a relatively new departure in endocrine therapy and should be engaged in under carefully controlled conditions. It was believed until recently, because of physiologic experiments, that the administration of testosterone induced atrophy of the testes although it stimulated the growth of the penis, scrotum, seminal vesicles and prostate as well as development of pubic and axillary hair. Shay and his coworkers[88] state, however, that under certain well-defined conditions immature germinal epithelium can be stimulated by testosterone propionate to increased activity. They found that the testes of treated animals contained more mature spermatozoa than those of controls. Curiously enough, they observed also that large doses of testosterone propionate caused less inhibition of growth and sperm maturation than did small doses. Jaffe and Brockway[89] report that testosterone propionate and methyl testosterone influenced favorably the growth of infantile genitalia in 5 of 7 boys. They observed the descent of a testis in only 1 of 5 cases of cryptorchidism. They also noted the increase in size of one atrophic testis. Moller-Christensen[90] favors chorionic gonadotropin for the treatment of cryptorchidism, but finds that a combination of the latter with testosterone is more effective. He found that boys from twelve to fourteen years of age responded most easily. Hamilton and Hubert[91] report findings in 20 true cryptorchids (8 bilateral, 12 unilateral) who were given testosterone propionate. The testes descended satisfactorily in the 8 bilateral cases, whereas the results were only partially successful in the 12 with unilateral retention. Zelson and Steinitz[92] and Wilson[93] confirm the fact that bilateral cryptorchids respond to therapy with androgens more satisfactorily than do unilateral cases. Wilson reports that 30 per cent of his cases reacted satisfactorily, and Zelson and Steinitz[92] found that 53 per cent of their cases were treated successfully with a combination of androgens and chorionic gonadotropin. Four of the 9 boys in their series had failed to respond previously to either one or the other of these preparations alone. The reviewer's unpublished experience with this form of therapy is encouraging thus far. Six cases of cryptorchidism or infantile genitalia in which chorionic gonadotropin had failed previously to elicit a favorable response, reacted strikingly to the administration of 10 to 12 mg. of testosterone propionate three times per week or 10 to 20 mg. methyl testosterone orally daily. The dose had to be adjusted in each case so that neither frequent priapism nor too rapid growth of the penis occurred; both of these are commonly encountered if too much hormone is given. The testes increased in size in every instance. In 1 case, which had responded only indifferently to chorionic gonadotropin over a period of eight months, the combination of the latter with testosterone propionate resulted in a rapid growth of the external genitalia and the appearance of a palpable right testicle where none had been felt previously. Boys undergoing this treatment showed an increased rate of growth and tend to lose the Fröhlich type of habitus (although it is possible that judicious dieting may play an important part in the latter result).

The androgens have been used in the treatment of peripheral vascular disease, angina pectoris and benign prostatic hypertrophy. Reports of such observations are still too few and too sketchy to warrant discussion in this review.

Certain gynecologic conditions have also been treated with androgens. Reports have appeared on its use in the menopausal syndrome, dysmenorrhea, premenstrual pain in the breasts, suppression of lactation and menometrorrhagia. Salmon,[94] Silberman, Radman and Abarbanel,[95] Nathanson and Towne[96] and Kurzrok, Birnberg and Livingston[97] have reported successful results in the treatment of the menopausal syndrome with testosterone propionate. Demarest,[98] Spence[99] and others have used the androgens for the relief of premenstrual pain in the breasts. Birnberg, Kurzrok and Klor,[100] Siegler and Silverstein[101] and

*The Perandren and Metandren used in these experiments were kindly furnished by the Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey.

Beilly and Solomon[102] have observed complete inhibition of lactation with this therapy. Rubinstein and Abarbanel,[103] Geist[104] and others have claimed a large measure of success in the use of androgens for the relief of dysmenorrhea. The androgens have apparently been used with success in the treatment of excessive bleeding due either to uncomplicated menorrhagia, metropathia hemorrhagica or uterine fibroids, according to the reports of a number of investigators including Loeser[105] and more recent ones by Sturgis, Abarbanel and Nader,[106] Huffman,[107] Greenhill and Freed[108] and Geist.[104] There is considerable difference of opinion concerning the amount of testosterone propionate necessary to control so-called "functional bleeding" and the mechanism by means of which it is accomplished. Some believe that testosterone inhibits the gonadotropic activity of the pituitary and thus reduces the secretion of the ovarian hormones; others suggest that it suppresses the secretion of the ovarian hormones at their source; and it is also thought that this androgen may have a direct inhibitory effect on the intermittent rhythmic contractions of the uterine musculature, thus reducing the amount of blood flow through the uterus.

The use of androgens for the treatment of certain gynecologic endocrinopathies has not been fully justified by its protagonists to the satisfaction of most clinicians. From this reviewer's viewpoint, the best one can say for the use of testosterone in the treatment of the menopause is that it represents an interesting physiologic experiment, which may lead to information concerning the pharmacology, physiology and biochemistry of the androgens. There appears to be no justification, however, for its use clinically except in occasional cases of excessive uterine hemorrhage, because the female sex hormone is more easily obtainable, is less expensive, can be given without the risk of inducing masculinity, and is physiologically more appropriate than testosterone. As a matter of fact, it would be desirable to adopt a conservative attitude toward the use of androgens in the treatment of most of the gynecologic endocrinopathies until sufficient time has elapsed to permit a more dispassionate appraisal of the situation under controlled experimental conditions. The widespread clinical use of androgens for such purposes is to be discouraged at present, but there is little doubt that further study will more clearly define the indications for the physiologic significance of successful androgen therapy in gynecologic disorders.

Synthetic oral and parenteral preparations of progesterone are available for clinical therapy, but a perusal of the literature leaves one in some doubt about the clinical indications for its use. Theoretically, from a physiologic viewpoint, it should be helpful in a number of conditions, and on this basis it has been recommended for the treatment of recurrent and threatened abortion, functional menometrorrhagia, dysmenorrhea, amenorrhea, and premenstrual breast tenderness. Many articles have been published in support of the use of progesterone in each of these conditions, but a high percentage of them are not critical enough of the experimental conditions on the basis of which the conclusions are drawn. Take, for instance, the extensive literature on the use of progesterone in habitual or threatened abortion, much of which is reviewed by Kotz, Parker and Kaufman.[109] With the exception of Campbell and Sevringhaus,[110] investigators of this phase of the subject, including Kotz and Parker, have claimed successful results with progesterone although they have routinely administered vitamin E and thyroid to each of their patients. The well-known salutary effects of each of these substances in habitual abortion are ignored for no apparent reason. Furthermore, the relatively small doses of 1 or 2 rabbit units of progesterone per week used by Campbell and Sevringhaus leave one wondering whether other factors did not have as much to do with the success they had in the handling of their cases. There is apparently no question that the percentage of patients who suffer from habitual or threatened abortion can be significantly decreased by an intelligent program that takes a number of pertinent factors into consideration, but to credit progesterone with each success would appear to be undesirable from a theoretical as well as a practical viewpoint.

Diethylstilbestrol, endocrine only through the courtesy of the physiologist, is a drug about which there is considerable controversy. It and the natural estrogens are not identical pharmacologically. Reynolds and Foster[111] have observed that even large doses of diethylstilbestrol do not cause an increase in the acetylcholine content of the uterus, whereas this does occur with the natural estrogens. In addition, DeWit and Bretschneider[112] have found that the drug does not cause the ovipositor reaction in female bitterlings, even when present in the water in lethal concentrations. Furthermore, diethylstilbestrol appears to be metabolized somewhat differently from the natural estrogens. The latter are largely destroyed in the liver, whereas the former is less affected by this organ and is eliminated to a much greater extent in the excreta, principally the urine (Zondek and Sulman[113] and Stroud[114]).

Advocates of the relative harmlessness of diethylstilbestrol point with complacent satisfaction to the well-recognized fact that the nausea, vomit-

ing and dizziness of certain so-called "sensitive persons" often disappear if therapy is continued in spite of these unpleasant symptoms. Forgotten is the additional fact that any toxic substance (for example, arsenic or nicotine) acts in a similar fashion. That is, a tolerance is built up that masks the objectively undesirable features of the drug. It should also be recalled that these toxic effects are induced by parenterally, as well as by orally, administered, stilbestrol. This indicates that the toxic effect is central. How much subtle damage (or lack of it) diethylstilbestrol may do over a period of years is as yet unknown, but in spite of this uncertainty too much of this drug is being prescribed without sufficient clinical indication just because it is relatively inexpensive and easy to obtain. Fortunately, the use of the natural estrogens has been curtailed for quite the opposite reasons.

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A review such as the foregoing is necessarily limited by the author's experience as well as by the extensiveness of the field. Nor has any attempt been made to include a discussion of all the contributions to each of the subjects that has been entertained. It is to be hoped that many of the important advances have been accounted for.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28471

PRESENTATION OF CASE

A fifty-year-old machine-shop foreman was admitted to the hospital because of back pain.

Approximately three months prior to admission the patient noted occasional "twinges" of aching pain in the left lumbar region. He found that sitting slumped down in the chair afforded some relief. He also obtained moderate temporary relief from adequate doses of aspirin, which he had taken during the entire illness. The pains gradually became more frequent and severe. Nine weeks before entry, severe pains developed in the left sacroiliac region and radiated down the inner aspect of the left leg, two thirds of the way to the knee; these forced him to give up his work. He compared the pain to that of sciatica, with which he had suffered for several years. At times, however, the pain radiated into the left groin and left upper quadrant and around under the left shoulder. He slept sitting up, because he found that he had less pain in this position. There was no pain associated with bending of the trunk or flexion or extension of the legs. Three weeks prior to admission he entered a community hospital, where the x-ray studies were said to have demonstrated arthritis and a slight curvature of the spine in the lumbar region. He was fitted with a supporting belt, which was said to have afforded some relief. During the two weeks before entry he had a fever ranging between 100 and 102°F. and his ankles became swollen. During the previous nine months he was said to have lost 30 pounds and to have developed a slight degree of exertional dyspnea. His appetite was good until nine weeks prior to admission, when it fell off markedly. No abdominal discomfort occurred on a moderate diet, but when he overate he suffered with gas and sour eructations, which became progressively worse. At no time did nausea, vomiting or diarrhea develop. He had always been quite constipated, for which he took enemas or Sal Hepatica. No changes were noted in the color of the stools.

Physical examination revealed a thickset, slightly pale man who was wheezing and belching but who did not appear to be in real distress. The heart was normal. Musical, dry rales and wheezes were audible throughout the chest. The abdomen was moderately distended and tympanitic. There were tenderness and spasm in the left upper quadrant, which prevented careful examination of a left upper-quadrant mass that descended with inspiration. At the left costovertebral angle there was slight tenderness. There was a right midsdorsal kyphosis and scoliosis, but the spine was flexible and there was no limitation of motion. Several fairly large hemorrhoids were felt on rectal examination. The prostate was moderately enlarged, smooth, firm and symmetrical, and was not tender.

The blood pressure was 130 systolic, 80 diastolic. The temperature was 100.5°F., the pulse 110, and the respirations 30.

The examination of the blood revealed a hemoglobin of 12.8 gm. and a white-cell count of 16,300 with 87 per cent polymorphonuclears. The urine was acid in reaction, had a specific gravity of 1.015 and gave a + test for albumin; the sediment contained a rare hyaline cast, 1 red cell and 5 white cells per high-power field. These findings were unchanged on repeated examinations. The blood Hinton test was negative. A van den Bergh was too low to read. The blood nonprotein nitrogen was 22 mg. per 100 cc., the calcium 12.7 mg., the phosphorus 2.6 mg., the phosphatase 8.1 Bodansky units, and the protein 5.1 gm. (albumin 2.6 gm. and globulin 2.5 gm.). A stool examination was negative for blood and mucus. The spinal-fluid pressure was 130 mm. (water) and the fluid contained 5 cells per cubic millimeter; the protein was 18 mg. per 100 cc., and the Wassermann test was negative. A Widal test, a heterophile-antibody test and an agglutination test for undulant fever were negative.

In an x-ray film of the chest there was mottled density in the left lower lung field and there appeared to be some pleural thickening in the left costophrenic angle; otherwise the lung fields were clear. Fluoroscopically, the changes in the left lower lung field appeared to be due to atelectasis and impaired aeration as a result of the elevated left diaphragm, which showed limitation of motion. The heart was not definitely increased in size. X-ray films of the spine showed slight degenerative changes about the lower thoracic and lumbar vertebras; otherwise there was no definite variation from the normal. In the gastrointestinal series only a small amount of barium was given because there appeared to be considerable gas in the bowel and the patient complained of rather severe constipation. The esophagus seemed normal. The mucosa of the stomach showed no definite evidence of ulceration, but there appeared to be pressure

on the posterior wall and lesser curvature from an extrinsic mass. The duodenal loop showed no definite evidence of a constant pressure defect except that the ligament of Treitz and the proximal loop of jejunum appeared to be displaced downward by the palpable mass in this region. The spleen was not definitely enlarged. In the intravenous pyelogram the kidney outlines were not well visualized. There was an area of calcification overlying the right transverse process of the third lumbar vertebra; the calyxes and pelvis on the right did not appear to be dilated. The area of calcification did not appear to be within the pelvis or ureter. There was a small amount of dye seen in the calyxes on the left; the kidney appeared to be definitely displaced downward, and there was a question of a pressure defect on the superior margin of the visualized calyxes. There was a small amount of barium remaining in the rectum. The bladder was not definitely abnormal.

An operation was performed on the ninth hospital day.

Differential Diagnosis

Dr. J. H. Means: This patient lost weight at a time when he had a good appetite. That always makes one think of thyrotoxicosis or diabetes, but as you will presently see there is no indication that this patient had either of these diseases. We are told nothing about his past history. Whether this is because it was not important or was not taken, I cannot say. In spite of the difficulty in palpating the abdomen because of tenderness, a mass was felt in the left upper quadrant but nothing much was determined about its size.

I am supposed to guess what the surgeon did and what he found.

This fifty-year-old man had a story, first, of nine months of weight loss and, then, of three months of pain, confined to his left side. The radiation suggests a phrenic-nerve distribution, possibly arising from the diaphragm. I am not sure how much of the radiation downward was due to the patient's illness on entry because he had had sciatica in the past; it is hard to tell how much of the pain was merely a continuation of that and how much was new. Apparently the patient had some difficulty in distinguishing between them. The impressive thing is that he had widespread radiation of pain both upward and downward on the left side.

On examination the most obvious thing is a mass in the left upper quadrant, which was apparently inflammatory, at least in part, because it was tender and gave rise to spasm both anteriorly and in the costovertebral region. This mass descended with inspiration. There was also some blood chemistry that requires careful consideration, which I shall take up a little later, but at the moment I shall ask Dr. Holmes to give me what help he can.

Dr. George W. Holmes: I can perhaps tell you some of the things it cannot be.

Dr. Means: I should like to learn all I can about the mass — where it is, how big it is, what shape it is, what its anatomic relations are and whether it involves the colon, kidney or spleen. I want to know if there is any evidence of tuberculosis in the chest, and all I can about the skeleton — whether there are any places giving a moth-eaten appearance that might suggest myeloma or metastatic malignant disease or tuberculosis.

Dr. Holmes: I am afraid you are going to be disappointed.

Dr. Means: If you rule them out that would be helpful.

Dr. Holmes: I shall take the chest first. There is a definite variation from the normal in the lower left lung field that has the x-ray appearance of localized atelectasis; such a condition might be due to the fact that the diaphragm is high on this side, pushed up by the mass below. I do not believe it is tuberculosis or any other active infection.

Dr. Means: Is there any evidence of tuberculosis elsewhere in the chest?

Dr. Holmes: No; he has thickened and rather peculiar looking lung markings in both sides of the chest.

Dr. Means: Has he got emphysema? He had some wheezing and musical rales.

Dr. Holmes: I can say the picture is consistent with emphysema but not that he actually had it. He has the increase in anteroposterior diameter often seen in emphysema.

Dr. Means: He probably had an emphysema, but I do not believe it is very important in the total situation.

Dr. Holmes: He has a normal-shaped heart, and no more change in the aorta than he has a right to have.

Dr. Means: Nothing abnormal in the mediastinum?

Dr. Holmes: No.

Dr. Means: What about the dorsal spine? Is that all right? He was fifty years old.

Dr. Holmes: The spine is not unusual for a man who has done heavy work up to the age of fifty. It is the spine you often see in old people or people with emphysema. From the films I do not believe that arthritis played a very important part.

Dr. Means: What about the mass in the abdomen?

DR. HOLMES: In the left upper quadrant is a rather indefinite area of dullness.

DR. MEANS: What about the kidneys and spleen?

DR. HOLMES: I cannot point them out on any of these films. I cannot even be certain of the mass, but I think there is a suggestion of it.

DR. MEANS: You are not sure he has a mass?

DR. HOLMES: No; but I think he has one.

DR. MEANS: This is very helpful in a negative way. At least, I believe it is.

I had various thoughts after studying this record. Certainly there was a mass. Dr. Holmes says there probably was one, and the man who did the physical examination says there was. I must accept as fact that there was a mass. Also, this mass was definitely tender and gave rise to spasm. We may say then that there was an inflammatory mass in the left upper quadrant. It was not spleen, and I get the impression from the various facts given that it might have been attached to the kidney, although probably it was not kidney alone. Since this malady began rather insidiously with pain, followed eventually by fever, and then there turned out to be a mass in the neighborhood of the left kidney, I thought first of a perinephritic abscess. As I pursued the abscess idea farther, the possibility of subphrenic abscess on the left side occurred to me. The diaphragm was high and atelectasis had been produced. Moreover there was pain that radiated to the left shoulder blade. I found it hard, however, to reconcile this diagnosis with the pain that radiated to the groin and flank and to the inner aspect of the leg. Therefore I thought of the possibility of psoas abscess arising from spinal caries of some sort. Dr. Holmes did not find any evidence of tuberculosis in the spine. By the way, Dr. Holmes, can you tell me something about the psoas muscles? Is there any evidence of psoas involvement?

DR. HOLMES: No.

DR. MEANS: I think we can therefore dismiss the possibility of psoas abscess, but there remain those of perinephritic or subdiaphragmatic abscess. What other possibilities are there? Could he have had anything arising from the splenic flexure of the colon? I suppose he could, but I do not know precisely what.

DR. HOLMES: There is pretty good evidence that there is no intrinsic disease of the colon.

DR. MEANS: Dr. Holmes says we can rule out the colon. That is very helpful.

I believe in all probability that the operation was exploration and drainage in the region of the mass. But there are a number of other points that we must consider before closing the matter.

The blood chemistry is interesting. A blood calcium of 12.7 mg. is above the upper range of normal. The phosphorus was on the lower border of normal. The phosphatase was definitely elevated. These findings make one think strongly of hyperparathyroidism, and yet I cannot make that diagnosis with any degree of assurance. I cannot reconcile it with the rest of the picture. There is no other evidence of hyperparathyroidism — no osteitis fibrosa cystica or any kidney lesion of the sort you get in hyperparathyroidism. I think the blood findings must be due to something else.

What else could they be due to? Multiple myeloma perhaps. The calcium may be elevated in this disease. I am also told, however, that the phosphorus is usually elevated. The serum protein in this patient was 5 gm., within normal limits, but on the low side. In myeloma it is usually elevated. Furthermore, there is no other evidence of myeloma. It is a very obscure disease and sometimes turns up at autopsy, not having been suspected in life. However, I think it is unlikely here.

I was intrigued by the weight loss, which preceded the rest of the illness by six months. A progressive loss of 30 pounds certainly cannot be laughed off, and always makes one think of some disease like tuberculosis, thyrotoxicosis or cancer.

I thought of the possibility of cancer of the kidney, and I wondered if one could get suppuration secondarily. Is it fair for me to ask?

DR. MALLORY: About a month ago we had a case of a large abscess inside a hypernephroma of the kidney.

DR. MEANS: I thought of that possibility here. It probably is not that though, because I thought of it.

Lymphoma is an insidious affair that also has to be thought of. I do not believe it is, although it could be. Certainly they would not have operated if they knew it was lymphoma, and even if it turns out to have been a tumor, I believe that there must have been some inflammatory process associated with it. I think, although I am by no means certain, that there is enough evidence to make a guess that he had an accumulation of pus and that this mass was an abscess. My first choice is a perinephritic one, and my second choice subdiaphragmatic.

I am quite prepared to be told that he had a cancer somewhere, but we have no evidence of metastasis anywhere in the body to help us on that. The prostate was said to have been enlarged, but the description of it does not sound like that of malignant disease. There is nothing in the gastrointestinal tract by x-ray examination, although he did have a few symptoms pointing in that direction. I do not believe he had hyperparathyroidism. What else could give him the changes observed

in the blood chemistry? He had been immobilized to some degree in a support, and Dr. Albright has shown us that immobilization will lead to rapid osteoporosis with atrophy of disuse of the bones and an outpouring of calcium. If the kidneys are not adequate, there is a high calcium but also a high phosphorus. This patient's kidneys were all right, so I think we may dismiss such an explanation. I am at a loss to explain the blood findings, and I am not going to attempt to explain them any more than I have indicated. I am content to say that I think we shall not be told that the surgeon explored this man's neck for a parathyroid tumor, and I expect that we shall be told that the operation was for the purpose of investigating the mass in the left upper quadrant. I believe that he found a perinephritic abscess, perhaps secondary to a carcinoma of the kidney.

DR. MALLORY: Have you anything further to add, Dr. Holmes?

DR. HOLMES: I should suspect that this patient's trouble was in the region of the upper pole of the kidney,—between it and the diaphragm,—and the first thing I should think of is a tumor arising from the kidney that became infected.

CLINICAL DIAGNOSIS

Retroperitoneal tumor?

DR. MEANS'S DIAGNOSIS

Perinephritic abscess, perhaps secondary to renal carcinoma.

ANATOMICAL DIAGNOSES

Carcinoma of body and tail of pancreas, with metastases to peritoneum, liver, mesenteric and retroperitoneal lymph nodes and lung and with extension to posterior portion of stomach.

Thrombosis of splenic and left main renal veins.
Pulmonary congestion and edema, minimal.
Hydrothorax, left, minimal.
Cholecystitis, chronic.
Cholelithiasis.
Arteriosclerosis: aorta, moderate, with calcification; pulmonary artery, moderate.
Healed pyelonephritis, right.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The operation was merely a peritoneoscopy. The preoperative diagnosis was cancer in the left upper quadrant. The surgeons did not commit themselves more closely than that. The possibilities of lymphoma and carcinoma of the pancreas were mentioned. Dr. Benedict, when he looked in, saw obvious cancer implants scattered over the peritoneal surfaces but was entirely unable to determine the primary site of the tumor.

The man went rapidly downhill, and when he came to autopsy, a huge tumor mass was found replacing the distal two thirds of the pancreas. The head of the pancreas was normal. The tumor was in such a place that it obviously did depress the duodenum, a fact that the radiologist spotted. It was large enough to have pressed on the pelvis of the left kidney, causing a little deformity, and also large enough to have elevated the diaphragm. It had invaded the serosa of the stomach but had not penetrated the muscular layers. There were extensive metastases in the liver, and one metastasis in the lower lobe of the left lung. The splenic vein was thrombosed, but the spleen was not enlarged and showed no evidence of infarction. The left renal vein was likewise thrombosed, and this kidney was enlarged, deeply congested and showed considerable tubular degeneration. The right kidney was small and deeply pitted with the scars of an old healed pyelonephritis. It is possible, therefore, that there was more renal insufficiency than was apparent from the clinical record. Unfortunately we were not informed of the chemical findings before we did the autopsy and did not investigate the parathyroid glands. The bone marrow, so far as examined, was negative.

CASE 28472

PRESENTATION OF CASE

First admission. A fourteen-month-old male child was admitted to the hospital because of generalized edema.

Two weeks prior to admission the child was found to have wet himself more frequently than usual. Ten days before, following a diarrhea for two days with loose, watery, brownish-green stools, the mother noticed puffiness about the eyes, which continued to the time of admission. Two days before, the abdomen became prominent and edema of the legs appeared. At that time, the child became "cranky." The family physician found albumin in the urine and therefore advised hospitalization.

The family and past histories were noncontributory.

Physical examination revealed a fat, fussy infant with edema about the eyes and slight edema of the lower extremities. The mucous membranes of the nose were somewhat pale and boggy. The eardrums were slightly thickened. There was some mucus in the posterior pharynx. The pharyngeal lymphoid tissue was slightly edematous. The examination of the lungs and heart was negative.

The abdomen was not prominent, and there was no edema in the abdominal wall or demonstrable ascites.

The temperature was 99°F., the pulse 90, and the respirations 20.

The urine had a specific gravity of 1.040 and gave a ++++ test for albumin. The sediment contained an amorphous albuminous precipitate, hyaline and fatty casts, occasional white cells and epithelial cells, and very rare red cells. The serum nonprotein nitrogen was 38 mg. per 100 cc., and the protein 3.9 gm.

On the second day the child's temperature was elevated to 101.5°F. Against advice the parents took the child from the hospital.

Second admission (four months later). The child was readmitted because of fever and diarrhea. One week before entry the patient had a slight head cold with a nasal discharge. Four days before, he fell out of the carriage, hit his head on the handle bar and had a brief nosebleed. Three days before, the child became feverish, the temperature ranging from 101 to 104°F. The next day diarrhea developed and there were as many as ten watery stools a day containing mucus and questionable small amounts of blood. During the three days of illness the patient's mother believed that the edema had diminished and that the urine volume had increased. During the twenty-four hours prior to entry, the family physician treated the patient with sulfanilamide.

Physical examination revealed a well-developed and well-nourished child who was acutely ill. He had a loose cough with some retraction of the chest with respirations. There was a contusion in the left temporal region, with some ecchymosis, and swelling about the eyes. The left eardrum was gray and shiny, with no fullness. The chest was resonant except for a questionable area of dullness at the right base posteriorly; no rales were audible. The diaphragms were high. Examination of the heart was negative. There was moderate distention of the abdomen, and a fluid wave with shifting flank dullness could be demonstrated. The child seemed to complain of pressure over the abdomen more than from a comparable degree of pressure on other parts of his body. Peristalsis was diminished. There was marked pitting edema of the scrotum and legs.

The temperature was 103°F., the pulse 123, and the respirations 20.

The examination of the blood revealed a red-cell count of 2,780,000 with a hemoglobin of 11.5 gm., and a white-cell count of 7400 with 61 per cent polymorphonuclears. The urine was acid in reaction, and had a specific gravity of 1.020, with a ++ test for albumin. The sediment contained frequent hyaline and finely and coarsely granular casts and 8 red cells, 5 white cells and 2 epithelial cells per high-power field. The stool was brown and guaiac positive. The serum nonprotein nitrogen was 28 mg. and the sugar 108 mg. per 100 cc. The blood sulfanilamide level on admission was 7.8 mg. per 100 cc. A stool culture was negative for pathogens. An x-ray film of the skull showed no definite evidence of fracture. A chest roentgenogram revealed some density in the medial portion of the left lung. A flat plate of the abdomen showed no evidence of dilated intestinal loops.

The sulfanilamide therapy was continued. The following morning the temperature had fallen to 101°F., but the respirations were still elevated. The child was taking fluids better and urinating, and during the day two stools of normal consistence were passed. Although the pulse was rapid, the quality was good, and there was no evidence of a disturbance in the peripheral circulation. Because of the fall in temperature, it was decided to delay shifting from sulfanilamide to sulfadiazine because of the greater danger of renal irritation and of anuria associated with the latter drug. The white-cell count was 6000, and the hemoglobin 10.1 gm. The sulfanilamide level was 9.2 mg. per 100 cc. The child was given a transfusion of 250 cc. of compatible whole blood.

During the course of the afternoon the temperature rose to 103°F. and the decision was made to substitute sulfadiazine for sulfanilamide therapy. In the early evening, abdominal distention increased and a rectal tube was inserted with some results. During the night some of the distention was relieved by belching and again by the rectal tube. At 7:00 in the morning the temperature was 101°F., the pulse and respirations were still elevated and the abdomen was still distended. The child had taken fluids in sips during the night without vomiting and had just voided. At 8:30 the nurse left the room for a few moments; on returning she found the baby had vomited and had ceased breathing.

Differential Diagnosis

Dr. William W. Beckman: Certain signs are present at both admissions of this child, and although the record does not state so specifically, I think it is safe to assume they were present in the interval between admissions. These were edema, albuminuria, cylindruria and hypoproteinemia, which constitute the most important features of the nephrotic syndrome, and I think one has to make that clinical diagnosis in this case.

The pathological diagnosis is somewhat more difficult because several types of renal pathology

have been found to be associated with the clinical entity known as the nephrotic syndrome. The first one reported was, I suppose, secondary syphilis. I do not believe that is important here for although there is no mention of any serologic test, there are no stigmas or other evidence of congenital syphilis, and nephrosis is such a very rare manifestation of syphilis that we do not have to consider it seriously.

Another not too uncommon cause of the nephrotic syndrome is intoxication with heavy metals, such as mercury. At the time of first admission one could have suspected that the child had taken mercury, unknown to the parents of course, because gastrointestinal symptoms, such as diarrhea, are typical of mercury intoxication. But a duration of four months with chronic nephrosis is too long for mercury intoxication, and we can rule it out on that basis.

The most difficult things to differentiate are the so-called "nephrotic stage" of glomerulonephritis and the "true nephrosis" of Volhard and Fahr. The only thing in favor of glomerulonephritis is the fact that there were red cells in the urine. Some writers say that if any red cells are present in the urine the diagnosis of nephrosis cannot be made. I think that is an extreme point of view, and I am sure there are published cases of true lipoid nephrosis with red cells observed some time in the course of the disease. Gross hematuria is rare, but a few red cells such as this are not sufficient evidence to rule out lipoid nephrosis. One datum that would be of interest and use in making the diagnosis of chronic nephritis is the blood pressure, but the pediatricians assure me that blood pressures of fourteen-month-old irritable infants are valueless. That has to be dispensed with in this case. I should also like to have evidence of nitrogen retention, as indicated by an elevated nonprotein nitrogen, to establish the diagnosis of glomerulonephritis. This child did have an elevated nonprotein nitrogen at the time of the first admission, but that could be accounted for on the basis that he probably was oliguric owing to the fact that he was forming edema at that time. The high specific gravity in the urine is further evidence of this. The nonprotein nitrogen of 38 mg. per 100 cc. was most probably due to urinary suppression. Then, on the second admission, the nonprotein nitrogen was within normal limits, whereas I should expect that, if this were chronic nephritis, the nitrogen retention would have progressed over the four months' period. So I think the best diagnosis for the underlying pathology is true lipoid nephrosis. There is one prominent feature of lipoid nephrosis that is not mentioned, namely, the blood lipids. In this hospital, we usually measure the cholesterol, which is elevated as all the lipids are.

DR. ALLAN M. BUTLER: It was not done.

DR. BECKMAN: That is one more constant feature of the syndrome. It may be present with chronic nephritis, but it always is with a true lipoid nephrosis. I think that diagnosis explains most of the things in this case except the terminal event. Diarrhea, which was a prominent symptom, is common in nephrosis, probably owing to edema of the intestines.

The cause of the final incident must be determined. If we assume that the child had lipoid nephrosis, we know that his resistance to infection was markedly diminished and certainly the terminal episode, on the basis of the fever, seems to have been infection, which is very hard to localize from the facts given in the abstract. The only lead from physical examination is that the abdomen was more tender than any other part of the body, but that is vague to say the least. There might be something in the x-ray films that would help.

DR. GEORGE W. HOLMES: I am afraid these x-ray films are not going to help much, except in a negative way. I do not see anything wrong with the chest. Some mention was made of a shadow on the left, but I do not see anything there that looks abnormal. The diaphragm is high, and the stomach is distended with gas. A film of the abdomen shows nothing remarkable and the skull films are negative.

DR. BECKMAN: Most infections in the course of lipoid nephrosis are caused by the pneumococcus. No bacteriologic data are given in the record except a stool culture, which was negative, but I should guess that this infection was probably due to a pneumococcus. On the basis of the fact that the abdomen was more tender than anything else, I should say there was a pneumococcal peritonitis. That is the commonest complication and commonest cause of death in nephrosis. Usually it is one of the higher types of pneumococcus, which inhabit the normal nasopharynx and which are rarely pathogenic except in a situation where resistance to infection is greatly diminished. The normal white-cell counts throughout the course of the illness are characteristic of nephrosis. That seems to be another manifestation of the diminished resistance to infection that these patients exhibit.

The actual mechanism of death I cannot make out, but I presume it was sepsis and that the same organism found in the peritoneum was found in the heart's blood at the time of autopsy.

DR. ROBERT R. LINTON: I notice that this child had a guaiac-positive stool. Has that any significance?

DR. BECKMAN: He had frequent diarrhea, perhaps with resulting irritation.

DR. BUTLER: This child is an example of the problem of intestinal distention in patients with nephrosis. The child with nephrosis that has no infection and no anatomic cause for intestinal obstruction often has an acute bout of gastrointestinal distention, sometimes with vomiting, but almost always with refusal of food and diminished peristalsis. When this particular child entered the hospital we pictured him as one who had an acute upper-respiratory infection, possibly with a peritonitis. The question whether or not peritonitis was present seemed quite doubtful, at least from the physical findings. Peristalsis was present, formed stools were passed, and the abdominal tenderness was not definite. On the first day he seemed to improve with sulfonamide therapy and the temperature came down. We were confronted with the dilemma of using the best drug for a possible pneumococcal infection, namely, sulfadiazine, or of being satisfied with a less effective drug, namely, sulfanilamide, to lessen the chance of causing renal irritation, since one always hesitates to give sulfadiazine or sulfathiazole to a patient who is very oliguric and already has renal difficulty. When the child did not seem to be so well, we decided to put him on sulfadiazine and did. The night preceding death, when the temperature went up and the distention increased, arrangements were made with the surgical service at 7:00 a.m. to tap the child to learn further about the organism causing the peritonitis, with the idea of giving type-specific serum if indicated. In a child like this, when there is a question of peritonitis and abdominal distention, the peritoneal tap should be done as a surgical procedure, since a blind tap may perforate a loop of distended bowel. In this particular case, unfortunately, the child died before this could be done. The sudden death illustrates another point about these nephrotic children. At the Children's Hospital there have been three sudden deaths in nephrotic patients when no serious infection appeared to be present. In fact, two patients did not appear critically ill, and yet within fifteen minutes they were found dead.

CLINICAL DIAGNOSES

Nephrosis.
Acute upper-respiratory infection
Pneumonia.
Peritonitis.
Edema and ascites.

DR. BECKMAN'S DIAGNOSES

Lipoid nephrosis.
Peritonitis (? pneumococcal).

ANATOMICAL DIAGNOSES

Lipoid nephrosis.
Peritonitis, generalized (streptococcal).
Anasarca.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: This child's kidneys were greatly enlarged, weighing 200 gm., which is about three times normal. The surfaces were generally pale and smooth, but there were focal bright-yellow spots scattered irregularly over the entire cortex. On the cut surface the cortex was very pale and rather mottled. Bright-yellow streaks could be made out in the pyramids, particularly at the points where the pyramids joined the cortex. This gross appearance made it evident that there must have been a great deal of lipid in the kidneys. Microscopically they are the type of kidneys over which pathologists love to debate whether they represent a subacute glomerulonephritis or true lipoid nephrosis. There is an extremely extensive tubular damage, with much lipid in the tubules, and also many collections of lipid in the histiocytes in the stroma. There are also some obviously abnormal glomeruli — individual glomeruli can be picked out — that are quite characteristic of a true glomerulonephritis. The majority of glomeruli, however, are quite negative, except for the presence of cells that are quite distended with lipids. Sometimes the lipid deposits seem to be in the endothelial cells of the capillaries, at other times in the epithelial cells overlying the surface of the tuft. Extensive lipid deposits in the glomeruli are not, to my mind, characteristic of the early stage of glomerulonephritis. I should personally classify this kidney as a lipoid nephrosis, not as a subacute glomerulonephritis, but I am quite sure that, if I put it up to a group of twenty pathologists, there would probably be about ten on each side of the question.

The peritoneum showed 800 cc. of cloudy exudate, and culture yielded alpha and beta hemolytic streptococci but no pneumococci. We were limited at autopsy to exploration of the abdomen so we cannot say what may have been present in the heart or lungs. I have an idea that even if we had done a complete autopsy we could not have explained the sudden episode.

DR. BUTLER: Streptococcal infection is often the cause of sudden death.

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MASSACHUSETTS MEDICAL SERVICE

Massachusetts Medical Service — the Blue Shield — became available to the public on Monday, November 16. Hailed by all as the contribution of the physicians to the health of the people of the State during a war crisis, when every man-hour is needed on the production front, the Blue Shield is now an actuality; and the eyes of the public are focused on the profession to see whether it can live up to the high promises of an entirely new type of service.

What the public does not and cannot know is the endless time and effort that antedated the present organization of the Blue Shield. For three years a special committee appointed by the Massachusetts Medical Society, the sponsor of the plan, studied similar projects both in this country and abroad, sifting each of them for the greatest merit. In the past few months, since the final plans were announced at the annual meeting of the Society on May 25, a large group of physicians, as well as industrial and business leaders, have given unselfishly of their time to make the Blue Shield a reality that would stand up under the test. Helping them was the State Commissioner of Insurance, who is well versed in the pitfalls of insurance practice.

There is no question that the new project will go down as history in medical annals. It will live not only for the service that it renders the public, but because the physicians of Massachusetts, despite the national crisis, were foresighted enough to offer a voluntary plan that helps to solve the growing problem concerning the equal distribution of medical care.

Massachusetts Medical Service began its operation with 2500 participating physicians. This is an impressive and adequate number, and one that foretells the success of the venture. Hundreds of additional signatures are needed, however, if the profession intends to go on record as a united group that is determined to solve medicoeconomic problems according to the principles of free practice and private initiative.

The profession can be justly proud of its achievement in launching Massachusetts Medical Service. Those who are not participants in this project, which is open to all licensed physicians in the State, should sign their applications without delay and return them to 230 Congress Street, Boston. In this manner, one hundred per cent of the physicians in Massachusetts can fulfill their role by standing solidly back of the forward-moving Blue Shield.

GASOLINE AND TIRE RATIONING

Elsewhere in this issue of the *Journal* is a copy of an open letter from the Gasoline Rationing Branch, Office of Price Administration, which was published in the "Medicine and the War"

section of the October 31 issue of the *Journal of the American Medical Association*.

By and large, there seems to be little need for calling physicians' attention to the things that they should do to conform to the regulations governing gasoline and tire rationing. Throughout the war effort, physicians have co-operated wholeheartedly: their response to the demands of the armed forces for medical officers has been superb; the needs of the Selective Service System and of the Office of Civilian Defense have been adequately met; and the increased activity occasioned by a depleted personnel in civilian and industrial medical practice has been cheerfully provided. Of course, as in any other group that represents a cross section of the general population, there are bound to be certain individuals who, because of carelessness, thoughtlessness or selfishness, will fail to "play the game." But these comprise a small minority, and the profession as a whole can be depended on to accept its responsibilities and to act according to standards that, throughout the years, have stood for patriotic and unselfish devotion to whatever cause, medical or otherwise, it has adopted.

MEDICAL EPONYM

Shiga–Flexner Bacillus

Kiyoshi Shiga (b. 1870), while assistant at Kitasato's Institute for Infectious Diseases, summarized his conclusions in regard to the bacillus of dysentery in an article, entitled "Ueber den Erreger der Dysenterie in Japan[The Causal Agent of Dysentery in Japan]," dated at Tokio, December 10, 1897. It was published in the *Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten* (*Abt.* I—**23**:599, 1898). He speaks of the failures of other investigators who had made use of animal experimentation, attributing this to the fact that most experimental animals are not susceptible to human dysentery. A portion of the translation follows:

> On this account, following the suggestion of Professor Kitasato, I have investigated the subject of dysentery from another angle, namely, as follows: The question arises whether one may not find a micro-organism in the stools of patients suffering with dysentery which will show an agglutinating reaction with their blood serum, such as Widal first demonstrated with typhoid bacilli and the serum of patients suffering with typhoid fever. I have made careful bacteriologic examinations of the stools and internal organs of 36 cases of dysentery, and have constantly found one and the same bacillus, which showed a clear-cut agglutinating reaction in the presence of serum of patients with dysentery. . . . I believe that we may probably consider this bacillus as the cause of dysentery.

He describes the cultural characteristics of the organism and further states that the serum of a person injected with the dead culture likewise shows the agglutinating reaction.

On April 12, 1900, Dr. Simon Flexner (b. 1863), professor of pathology at the University of Pennsylvania, delivered a lecture before the New York Pathological Society, entitled "On the Etiology of Tropical Dysentery." This was published in the *Bulletin of the Johns Hopkins Hospital* (**11**: 231-242, 1900). After an exhaustive account of his investigations and a complete review of the symptomatology, bacteriology and pathology of tropical dysentery, including reference to Shiga's work, he concludes:

> I think I have shown that tropical dysentery consists of a bacillary and an amebic form, separable in their early and their later stages by their clinical histories, their etiology and pathological anatomy.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Analysis of Causes of Maternal Death in Massachusetts during 1941

Embolism

As the tabulation that appeared in the October 15 issue of the *Journal* showed, 39 cases were allocated to embolism as the primary cause of death, and this number is exceeded only by those deaths attributed to sepsis and medical causes.

Five cases were associated with cesarean section. The first was that of an elderly primipara, who after a classical section ran a slight temperature until the thirteenth day, when there were definite pain and redness in the calf of one leg. Twenty minutes later, following an attack of cyanosis and dyspnea, the patient became pulseless and expired. This embolus undoubtedly originated from a pelvic thrombophlebitis.

The second case was associated with a placenta previa. This patient had had no prenatal care until the eighth month, when she summoned a physician because of painless bleeding. The section was followed by a supravaginal hysterectomy.

Sepsis developed postoperatively; and although sulfonamide therapy was instituted and several transfusions were administered, death occurred suddenly following an acute pain in the chest on the twenty-eighth day after delivery. The supravaginal hysterectomy was done because of a very adherent placenta, which was described as an accreta.

The third case was that of a multipara who had had a marginal placenta previa diagnosed by vaginal examination; because of the resulting bleeding a cesarean section was immediately done under spinal anesthesia. Forty minutes after the beginning of the operation the patient suddenly became blue and died. This was probably an embolic death, although no autopsy was performed.

The fourth patient, who had had a previous cesarean section, died very suddenly shortly after the operation. There was no history of hemorrhage, and the diagnosis of embolism is undoubtedly correct.

The fifth case was also a repeat cesarean section, which was followed by a normal convalescence until the fourteenth day, when the patient developed a pain in her chest; three days later, while combing her hair, she slumped in the chair and died immediately. Undoubtedly this was a true case of embolism.

There were 10 cases in this series associated with operative vaginal delivery. The first occurred in a thirty-year-old multipara with twins and is an example of poor obstetrics. Labor did not start until the fifth day after premature rupture of the membranes, and attempts at forceps delivery and then at version were unsuccessful, a diagnosis then being made of a hydrocephalic baby, which was finally delivered by craniotomy. The second baby was delivered easily. Infection resulted, and in spite of sulfonamide therapy and intravenous injections of plasma, death occurred suddenly on the twentieth day after delivery. It is quite likely from the history that the infection involved the peritoneum, which suggests a possible rupture of the uterus.

The second case was associated with premature separation of the placenta, which was treated by hysterectomy. The patient was transfused four times. Infection developed, and in spite of hemotherapy, death occurred precipitately six days postoperatively. The prenatal care in this case was inadequate, the patient having been seen only once before the catastrophe; but it is doubtful whether prenatal care would have averted this fatality.

The third case was that of a patient who was delivered at home by low forceps but was moved to a hospital because of the occurrence of an embolus prior to delivery of the placenta and died shortly after entry. Emboli during labor are fortunately uncommon. It is difficult to know how such a death could have been averted.

The fourth death occurred in a woman who had had six previous full-term deliveries and whose history indicated a long period of irregular bleeding. Four weeks before hospital entry a curettage had been done, the pathological report of these curettings being "necrotic placental tissue." On re-entry, because of the bleeding and the size of the uterus, which was diagnosed as a fibroid, a hysterectomy was performed and death occurred suddenly ten days postoperatively. The uterus, when opened after operation, revealed a three-month fetus. A mistaken diagnosis, of course, was the real cause of this sad catastrophe.

The fifth case was that of a patient delivered by low forceps who went into shock shortly after delivery. She was given 2 ampules of blood plasma, but death occurred shortly afterward. Postmortem uterine palpation showed the uterus to be intact, thus ruling out rupture of the uterus. There was no history of a difficult anesthesia. Although no autopsy was performed, the suddenness of the death makes it likely that embolism was the true cause.

The sixth case was that of a multipara with six living children who, when about seven months pregnant, entered a hospital because of bleeding and presented a picture of complete separation of the placenta. The cervix was said to be dilated to admit three fingers, an easy version was done, and the patient's pulse at the end of operation was 86. Two hours post partum, however, she suddenly became cyanotic and died. It is most likely that embolism was the cause of this death because of its extremely sudden nature, but it is also possible that the version resulted in rupture of the uterus.

The seventh case was that of a multipara who suddenly became pulseless and cyanotic during labor. She was delivered by high forceps but died half an hour after delivery, and pulmonary embolism seems the most likely cause of death.

The eighth patient was an obese woman with large varicosities of the vulva and thighs who was delivered by low forceps; she died six hours after delivery, following an attack of cyanosis and respiratory distress, before a physician could get to her.

The ninth patient ran a slight temperature following a low-forceps delivery; on the eighth postpartum day a sharp pain developed in the left thigh and was followed almost immediately by cyanosis and death. This embolus was septic in origin.

The tenth case was that of a patient who had been delivered by simple low forceps nine days previous to a cholecystectomy, which was performed for an acute cholecystitis. She had an uneventful convalescence until the seventh postoperative day, when she collapsed, became cyanotic and died within fifteen minutes. Pregnancy in this case was merely incidental; death was due to pulmonary embolism following cholecystectomy.

(*To be concluded*)

DEATHS

GEORGE — Leslie H. George, M.D., of Haverhill, died October 25. He was in his sixty-fourth year.

Born in Dorchester, he attended Clark University and the College of Physicians and Surgeons, Columbia University, and received his degree from Maryland Medical College in 1905.

Dr. George was a former member of the Massachusetts Medical Society and of the staff of Gale Hospital, Haverhill.

TUTTLE — George H. Tuttle, M.D., of South Acton, died April 2. He was in his seventy-seventh year.

Dr. Tuttle received his degree from the Harvard Medical School in 1891. He was a member of the Massachusetts Medical Society and the American Medical Association.

WAR ACTIVITIES

OFFICE OF PRICE ADMINISTRATION

Gasoline and Tire Rationing

The following open letter to all physicians of the United States was recently released by the chief of the Gasoline Rationing Branch, Office of Price Administration:

In the East Coast gasoline-rationing program, made necessary by the shortage of transportation facilities for petroleum products, the indispensability of your profession was recognized by its inclusion in the categories of persons eligible for preferred mileage, that is, necessary occupational mileage in excess of 470 miles a month. Now the Office of Price Administration has been ordered by Mr. William Jeffers to institute and administer a nationwide mileage-rationing program for the express purpose of conserving our rubber-borne transportation. In framing the regulations for the new program, your profession was one of the first to be provided for.

If we are to carry out our double task of preventing a collapse of our military and civilian transportation, we must have the complete co-operation of those groups of persons whose driving is deemed essential to the war effort. Our immediate aim is to attain the 5000-mile national mileage average set by the Baruch Report as the maximum possible in light of the dire rubber shortage. Our experience with the East Coast program tells us that the preferred categories use one half the gasoline consumed, though they constitute less than one fourth the total number of automobile operators. Clearly, then, the great savings of rubber on a nationwide scale must be made in the preferred categories.

Under the regulations governing the mileage-rationing program, physicians are eligible for preferred mileage if their essential occupational needs exceed 470 miles a month and if the mileage is needed for regularly rendering necessary professional services. Mileage traveled daily or periodically between home or lodging and a fixed place of work is not considered preferred. Physicians who conduct their practices in offices, as many specialists do, are not eligible for preferred mileage.

Without question or hesitation, doctors have been and will be granted all the gasoline needed to carry out their professional work. We hope that they will regard their concrete symbol of their indispensability, the C book, as a moral obligation and not as a personal privilege. From another point of view, the C book is part of a doctor's equipment; it should not be used for anything but the work of humanity.

When nationwide gasoline rationing begins, there are certain concrete things a doctor can do to live up to the high ethical standards set for him by his own profession:

(1) At the time of first issuance of rations, he can so carefully compute his necessary mileage as to make a B book adequate for his purposes though he might easily make out a case for a C book, which might be granted to him without question by his local war-price and rationing board, eager to provide for physicians.

(2) In the computation of his mileage, he can religiously adhere to the provision of the regulations, which makes 150 miles of his basic ration available for occupational purposes. Moreover, he can help mightily in establishing the principles that only 90 miles of the basic ration are to be used for home necessary use and that there is no provision whatever in any ration for "pleasure driving."

(3) Conversely, if he should be granted a C book, he can return to the local board, at the end of the three-month period, all unused coupons accruing to him as a result of a quite natural overestimation of needs or of overgenerous "tailoring" by his board, instead of using such coupons for nonessential purposes. The moral effect of such an act on his fellow citizens will be incalculable.

(4) He can set an example by scrupulously observing the 35-mile speed limit, except in cases of emergency, in spite of the fact that doctors could easily "get away with it."

(5) Should he be assigned to a hospital, clinic or institution after a ration card for calling on his private practice has been issued, he can use public means of transportation at the price of personal inconvenience.

(6) He can refrain from any kind of driving whatever that might appear to be nonessential in the eyes of the public.

Doctors are the leaders and molders of public opinion in their communities. If the average man has any reason to believe that the professional men whom he regards with great respect are indifferent or hostile to the mileage-rationing program, it will be difficult, if not impossible, to make it effective. Conversely, if doctors as a group observe the letter and spirit of the regulations, they will be a powerful force in making this absolutely mandatory war measure serve its pur-

pose. We know that we can rely on the support of your profession, which has demonstrated its patriotism, ability and unselfishness at every opportunity.

JOHN R. RICHARDS
Gasoline Rationing Branch
Office of Price Administration

MISCELLANY

RÉSUMÉ OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR SEPTEMBER, 1942

Diseases	September 1942	September 1941	Five-Year Average*
Anterior poliomyelitis	9	66	49
Chicken pox	105	106	89
Diphtheria	11	10	9
Dog bite	870	1153	954
Dysentery, bacillary	6	110	44
German measles	69	28	21
Gonorrhea	521	403	450
Measles	150	168	127
Meningitis, meningococcal	7	8	4
Meningitis, other forms	3	2	†
Mumps	248	233	133
Paratyphoid infections	33	2	10
Pneumonia, lobar	193	106	110
Scarlet fever	316	243	155
Syphilis	460	361	408
Tuberculosis, pulmonary	276	229	243
Tuberculosis, other forms	18	23	24
Typhoid fever	4	7	10
Undulant fever	4	8	4
Whooping cough	778	546	466

*Based on figures for preceding five years.
†Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from: Amherst, 1; Boston, 2; Fitchburg, 1; Holyoke, 1; Somerville, 1; Stoneham, 1; Weymouth, 1; Williamstown, 1; total, 9.

Diphtheria was reported from: Arlington, 1; Boston, 1; Bourne, 1; Fall River, 6; Lowell, 1; Wrentham, 1; total, 11.

Dysentery, bacillary, was reported from: Boston, 2; Lynn, 1; Salem, 3; total, 6.

Encephalitis, infectious, was reported from: Lowell, 1; Northampton, 1; total, 2.

Malaria was reported from: Arlington, 1; Boston, 1; Camp Edwards, 4; total, 6.

Meningitis, meningococcal, was reported from: Boston, 1; Cambridge, 1; Melrose, 1; New Bedford, 1; West Springfield, 1; Weymouth, 1; Worcester, 1; total, 7.

Meningitis, other forms, was reported from: Avon, 1; Plymouth, 1; Randolph, 1; total, 3.

Paratyphoid infections were reported from: Andover, 1; Boston, 11; Brockton, 1; Cambridge, 3; Framingham, 1; Greenfield, 2; Hull, 1; Mansfield, 1; Quincy, 4; Salem, 1; Somerville, 2; Walpole, 1; Waltham, 4; total, 33.

Septic sore throat was reported from: Boston, 1; Cambridge, 1; Fort Banks, 1; Ipswich, 2; Williamstown, 1; total, 6.

Tetanus was reported from: Plymouth, 1; Springfield, 1; total, 2.

Trachoma was reported from: Boston, 1; total, 1.

Typhoid fever was reported from: Arlington, 1; Everett, 1; Gloucester, 1; Pittsfield, 1; total, 4.

Undulant fever was reported from: Blandford, 1; Chatham, 1; Mattapoisett, 1; Somerville, 1; total, 4.

Weil's disease was reported from: Boston, 1; total, 1.

Communicable diseases reported at figures above their respective five-year averages were chicken pox, diphtheria, measles, meningococcal meningitis and lobar pneumonia.

Record-high figures were attained for German measles, paratyphoid infections, whooping cough and mumps. The latter, after a month's drop from record figures, is back again in the record column for the thirteenth time during the past fifteen months.

Diseases reported at figures below their five-year incidences were anterior poliomyelitis, dog bite and bacillary dysentery.

Typhoid fever and tuberculosis, other forms, were reported at record-low incidences.

Undulant fever was reported at a figure equal to its five-year average.

Two cases of animal rabies were reported from the focus in the northeastern section of the State.

CORRESPONDENCE

ROTATING INTERNSHIPS

To the Editor: To prepare physicians for war service, the members of the Medical Staff of the Salem Hospital are convinced that the rotating internship, with a knowledge of the Army and Navy requirements for young doctors, is a responsibility of hospitals today. It is not fair to a young doctor to place him in the Army or Navy without certain basic training that will enable him to meet emergency conditions that he might be called on to meet unaided.

The Salem Hospital has offered rotating internships for many years and has been accredited for the training of interns by the American Medical Association since accreditation was first offered. Both the administrative office of the hospital and its medical staff have taken this job very seriously.

Although we have endeavored to give each intern instruction and practice in all departments, eighteen months, or even two years, is too short for any of them to become expert in any one department. We have therefore tried to impress on them that if they wish to become specialists in any branch of medicine, they should seek a further internship or residency devoted exclusively to the specialty of their choice. This, many of them have done.

Now the war has changed all that, and the young doctor must get the most he can out of a one-year internship and we must see to it that he does. Whether it is worth while to help an intern through an occasional appendectomy or hernia or give him instruction in spinal anesthesia during that short service has been, and still is, a much-disputed problem. Some men react quickly and seem to profit; with others, one feels that the time spent is wasted. However, we have given them the benefit of the doubt and offered that instruction.

An incident that recently came to our notice encourages us to believe that at least during the emergency this is the right thing to do, and seems worth reporting. One of our interns who graduated last June immediately enlisted in the Navy. In due course of time, he was assigned as medical officer to a vessel and sent to sea in company with other naval ships. During the voyage, a seaman in an accompanying ship developed acute appendicitis. The medical officer of that ship had had a straight medical internship and knew little or nothing about operating. The commanding officer therefore transferred our ex-intern to that ship in mid-ocean, where he was able to give the seaman spinal anesthesia and to remove successfully the of-

fending appendix. The sailor had a speedy and uneventful convalescence.

This episode is offered with all due modesty as an informative rather than a laudatory message.

WALTER G. PHIPPEN, M.D., *President*
Medical Staff
Salem Hospital
Salem, Massachusetts

MEDICAL EDUCATION OF THE PUBLIC

To the Editor: Permit me to commend you for the stand you take in relation to such articles as the one published in *Reader's Digest* regarding the "one-day cure for syphilis." There may be grave consequences from publication of such unfinished investigations; certainly not much good will be accomplished. Contradiction or even discussion serves only to attract the attention of the morbidly curious or innocently interested portion of the public. However, I do not expect that your editorial nor my feeble protest will have any effect on a magazine which is inclined to print that brand of "literature."

"Married Love" and "Should My Boy Be Circumcised" might be quite appropriate in a medical journal but to my way of thinking are decidedly out of place in a widely read and indiscriminately circulated magazine such as the one that published them, especially one that caters to and seeks actively a circulation among school children.

I know, because I have tried, how little effect criticism has upon such publishers. As a defense, for instance, I was informed that one of the articles was timed so as to appear in a summer-time issue when the schools were not in session. So I have become a trifle more circumspect in selecting reading matter for my office as well as for my home.

JOHN V. GALLAGHER, M.D.
Milford, Massachusetts

REPORT OF MEETING

BOSTON CITY HOSPITAL
HOUSE OFFICERS' ASSOCIATION

At the first of a series of meetings on war medicine, sponsored by the Boston City Hospital House Officers' Association, Dr. Harold W. Brown, dean of the School of Public Health at the University of North Carolina, spoke on "Parasitic Disease Prevalent in the African and Pacific Theaters of War."

The chief problem in the management of tropical diseases is the institution of therapy at an early date to prevent the otherwise chronic and disastrous sequelae of most of these infections. The aim, then, should be to sharpen one's diagnostic acumen in these diseases, which heretofore have merely been a textbook picture to most physicians. To prevent or decrease the number of cases, one must be acquainted with the source of the infection, the vectors involved in its transmission, and the habits of man that make infestation possible. The problem is not confined to the actual theaters of war, for these diseases on the whole are not self-limited and may be brought home by returning troops, where they may cause disease in the civilian population. Some parasites may even become indigenous in this country if the proper vector is present and the habits of man are favorable for its perpetuation. But many of the fears so far expressed are probably unfounded, for most of the parasitic diseases brought back will disappear through death of the parasite, host or vector.

One of the common conditions encountered in the tropics is filariasis, most commonly caused by *Filaria bancrofti*. This is found in this country only in Charleston, North Carolina, but is very prevalent in North Africa, India, the Pacific islands and Australia. As an example, 15 per cent of the inhabitants of the Solomon Islands have elephantiasis and many more must harbor the parasite. Transmission is accomplished by the female of all genera of mosquitoes, in distinction to malaria. The microfilaria enter the blood stream and muscle of the insect from the alimentary tract and thence migrate to the proboscis in the course of a few weeks, where they are ready for reinjection into the host. They are found in the blood stream in greatest numbers and sometimes only during the night, so smears should be taken at that time. They require about a year to mature in the blood stream of the host. They then find their way to the lymph channels where they reproduce. Although many people infected with the parasite show no symptoms, recurrent lymphangitis and elephantiasis are frequent late manifestations. Recurrent lymphangitis may be caused by the death of the parasites and the absorption of some toxic substance. Elephantiasis may be initiated and certainly can be continued in the absence of any filaria. There seems to be an original lymph stasis, which is perpetuated in some unknown manner. Streptoccocal infection may play a major or minor role, according to various observers. Although 95 per cent of elephantiasis occurs in the lower extremity, the scrotum, vulva and breasts are not uncommon sites for the condition. Treatment of this group of diseases has so far been unsatisfactory, arsenical and antimony compounds being the drugs most widely employed. There is some question concerning the efficacy of killing the parasites, since this may initiate either of the late manifestations mentioned above. Although this condition has been present in Charleston for a century, there has been no spread, so we may be fairly confident that it will not assume any great proportions in this country.

The second large group of parasites are the schistosomes, which live in the blood vessels of man and produce symptoms referable to the site of predilection of each species. *Schistosomum hematobium*, which invades the vessels of the urinary bladder, is distributed widely in North Africa, and over 50 per cent of the population of Egypt is infected. *S. mansoni* is also found in that region as well as in South America and some of the Pacific islands. Its site of predilection is the liver and portal system, where it causes ascites, various abdominal complaints and great emaciation. *S. japonicum* is most prevalent in Japan but is also found in certain sections of the China coast. Transmission is from man to water snail to man. The eggs must fall in water, where the miracidial form is taken up by the snail. Here the development takes place whereby the cercarial form is attained, and this then enters the human host. Spines aid in the penetrating tactics of the parasites, but there is some question whether a lytic fluid is secreted. The adult form lives in man, and the fact that the eggs must fall in water may prevent the transmission of the disease in this country. The same genus is found here, but for some reason these snails do not seem to be satisfactory as a vector. The conditions favoring the spread

in Asiatic and African countries, which do not obtain here, are the use of human feces for fertilizer (Asia) and defecating in or near water (Egypt).

The trypanosomes comprise one of the largest groups of pathogenic parasites. They are widely distributed in the areas where troops are now engaged in combat, and cause sleeping sickness and Chagas's disease. *Trypanosoma gambiense*, *T. rhodesiense* and so forth, which were formerly considered different, are probably the same species with various reactions dependent on the immunologic background of the host. The tsetse fly is the only known vector, and it is not found in this country; but the black (biting) stable fly of this country can mechanically transmit the parasite. Therefore the disease is possible but not very probable here. Chagas's disease, in South America, is transmitted by the *Glossina palpalis*. The cycle in the fly requires several days. Reservoirs or natural sources of these diseases are found in some antelope. Formerly as many as 50 per cent of the population of a community died each year with trypanosomiasis. The early manifestations include a rash, enlargement of the posterior cervical lymph nodes and orbital edema. At autopsy the brain usually reveals a typical nonspecific perivascular cuffing. There are two forms of treatment. The first is Bayer 205 (Germanin), which is administered intravenously. The initial dose is 0.3 gm., to test the sensitivity of the patient; if no untoward effects result, this is followed by the therapeutic dose — 1.0 gm. in 10 cc. of fluid, to a total of 10 gm. There are a considerable number of reactions, some of which are fatal. Tryparsamide and other arsenicals are also employed. The former is given in a dose of 0.045 gm. per kilogram of body weight for eight to fifteen weekly injections. The main complication following the use of this drug is optic atrophy.

Other parasites commonly encountered in the tropics are the *Leishmania*. *Leishmania donovani*, found in North Africa, Asia, India and China, causes the visceral form of kala-azar. *L. tropica*, found in about the same sectors, causes a cutaneous form of the disease called Oriental sore. *L. braziliensis* also causes a cutaneous form and is prevalent in South America and even Central America. The vector is presumed to be phlebotomus, which is able to pass through most mosquito netting. It is also found in bedbugs but apparently cannot be transmitted by them. In this country the responsible mosquito is found only on Plummer's Island, off the coast of Maryland. The parasite is found in the leukocytes in man. The clinical manifestations of the visceral type are an enlarged abdomen from hepatomegaly and splenomegaly; of the cutaneous type, a chronic moist ulcer; and of the South American form, mucous-membrane lesions as well as cutaneous sores. Treatment of leishmaniasis was formerly carried out with potassium and sodium antimony tartrate, but these have now been supplanted by the pentavalent antimony compounds, such as Neostibosan. The cutaneous forms are treated by these drugs, but also receive irradiation and carbon dioxide snow.

In summary, Dr. Brown emphasized that although the habits and the lack of suitable vectors militate against endemic foci of these tropical diseases in this country, occasional cases will be brought back that have been misdiagnosed or inadequately treated. It was pointed out in passing that, although malaria is now endemic in this country in mild form, more severe forms may be brought back to plague a nonresistant host.

BOOK REVIEWS

Roentgen Treatment of Infections. By James F. Kelly, M.D. With the collaboration of D. Arnold Dowell, M.D. 8°, cloth, 432 pp., with 122 illustrations and 25 tables. Chicago: The Year Book Publishers, Inc., 1942. $6.00.

The title of this book suggests that it is a discussion of the roentgen treatment of all the various types of infectious process in which such treatment has been found of value. Actually its main thesis concerns the roentgen treatment of gas gangrene. To the reviewer it seems that all the pertinent facts concerning the treatment of that condition might have been clearly set forth in a treatise of some 25 pages, but instead the authors ramble on through slightly more than 400 pages.

The first two chapters, amounting to about 100 pages, comprise a very elementary discussion of the early history of roentgenology, the physics of roentgenology and roentgen dosage. This discussion adds little to the value of the book.

The authors point out that the mortality from gas gangrene at the close of the last century was 50 per cent and that this rate continued through World War I and up to 1928, when roentgen treatment was first used. In their most recent series of 42 cases the rate was reduced to 5 per cent. They are opposed to the use of serum and also to the use of sulfanilamide and related compounds. They believe that débridement should be carried out only after several days of roentgen therapy, since much of the tissue that is at first discolored will later regain full vitality. The dosage recommended is about 70 r twice daily for two or three days and then once daily for several more days. The total dose rarely exceeds a threshold erythema.

There are somewhat shorter discussions of the treatment of such conditions as peritonitis, carbuncles, parotitis, mastoiditis and pneumonia.

The History and Evolution of Surgical Instruments. By Dr. C. J. S. Thompson. With a foreword by Dr. Chauncey D. Leake, M.D. 4°, cloth, 113 pp., with 115 illustrations. New York: Schuman's, 1942. $8.50.

This book is an excellent general historical survey of the surgeon's tools from the paleolithic period to the beginning of the present century. The author bases his discussion on the famous collection of surgical instruments in the possession of the Royal College of Surgeons, of which he was curator. Excellent reproductions and descriptions are given of scalpels, amputation knives, saws, trepans, vaginal dilators and speculums, head saws, artery and dressing forceps, bullet-forceps and extractors, instruments for phlebotomy and venesection, tourniquets, trocars and operating tables. The author makes special note of the famous surgeons who used these instruments.

The value of this book is measurably increased when one reads the following words: "We have suffered a grievous calamity in the almost total loss of our incomparable collection of surgical instruments at the Royal College of Surgeons. High explosives reduced the interior of the museum to ruins and the historical instrument rooms were burnt out. It is a terrible loss as only a few specimens were saved." This book is worthy of being owned by all surgeons and should of course be in every library.

(Notices on page xiv)